Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the anti-TAT antibody or TAT polypeptide coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding anti-TAT antibody or TAT polypeptide.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of anti-TAT antibody or TAT polypeptide in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Culturing the Host Cells

The host cells used to produce the anti-TAT antibody or TAT polypeptide of this invention may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), (Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham et al., Meth. Enz. 58:44 (1979), Barnes et al., Anal. Biochem.102:255 (1980), U.S. Pat. Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO 90/03430; WO 87/00195; or U.S. Patent Re. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as GENTAMYCIN™ drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

5. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence TAT polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to TAT DNA and encoding a specific antibody epitope.

6. Purification of Anti-TAT Antibody and TAT Polypeptide

Forms of anti-TAT antibody and TAT polypeptide may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of anti-TAT antibody and TAT polypeptide can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify anti-TAT antibody and TAT polypeptide from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the anti-TAT antibody and TAT polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular anti-TAT antibody or TAT polypeptide produced.

When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, are removed, for example, by centrifugation or ultrafiltration. Carter et al., Bio/Technology 10:163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being the preferred purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used

to purify antibodies that are based on human γ1, γ2 or γ4 heavy chains (Lindmark et al., J. Immunol. Meth. 62:1-13 (1983)). Protein G is recommended for all mouse isotypes and for human γ3 (Guss et al., EMBO J. 5:15671575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_H3 domain, the Bakerbond ABX™resin (J. T. Baker, Phillipsburg, NJ) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSE™ chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5-4.5, preferably performed at low salt concentrations (e.g., from about 0-0.25M salt).

J. Pharmaceutical Formulations

Therapeutic formulations of the anti-TAT antibodies, TAT binding oligopeptides, TAT binding organic molecules and/or TAT polypeptides used in accordance with the present invention are prepared for storage by mixing the antibody, polypeptide, oligopeptide or organic molecule having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as acetate, Tris, phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; tonicifiers such as trehalose and sodium chloride; sugars such as sucrose, mannitol, trehalose or sorbitol; surfactant such as polysorbate; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG). The antibody preferably comprises the antibody at a concentration of between 5-200 mg/ml, preferably between 10-100 mg/ml.

The formulations herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, in addition to an anti-TAT antibody, TAT binding oligopeptide, or TAT binding organic molecule, it may be desirable to include in the one formulation, an additional antibody, e.g., a second anti-TAT antibody which binds a different epitope on the TAT polypeptide, or an antibody to some other target

such as a growth factor that affects the growth of the particular cancer. Alternatively, or additionally, the composition may further comprise a chemotherapeutic agent, cytotoxic agent, cytokine, growth inhibitory agent, anti-hormonal agent, and/or cardioprotectant. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT® (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

K. Diagnosis and Treatment with Anti-TAT Antibodies, TAT Binding Oligopeptides and TAT Binding Organic Molecules

To determine TAT expression in the cancer, various diagnostic assays are available. In one embodiment, TAT polypeptide overexpression may be analyzed by immunohistochemistry (IHC). Parrafin embedded tissue sections from a tumor biopsy may be subjected to the IHC assay and accorded a TAT protein staining intensity criteria as follows:

Score 0 - no staining is observed or membrane staining is observed in less than 10% of tumor cells.

Score 1+ - a faint/barely perceptible membrane staining is detected in more than 10% of the tumor cells. The cells are only stained in part of their membrane.

Score 2+ - a weak to moderate complete membrane staining is observed in more than 10% of the tumor cells.

Score 3+ - a moderate to strong complete membrane staining is observed in more than 10% of the tumor cells.

Those tumors with 0 or 1+ scores for TAT polypeptide expression may be characterized as not overexpressing TAT, whereas those tumors with 2+ or 3+ scores may be characterized as overexpressing TAT.

Alternatively, or additionally, FISH assays such as the INFORM® (sold by Ventana, Arizona) or PATHVISION® (Vysis, Illinois) may be carried out on formalin-fixed, paraffin-embedded tumor tissue to determine the extent (if any) of TAT overexpression in the tumor.

TAT overexpression or amplification may be evaluated using an *in vivo* diagnostic assay, e.g., by administering a molecule (such as an antibody, oligopeptide or organic molecule) which binds the molecule to be detected and is tagged with a detectable label (e.g., a radioactive isotope or a fluorescent label) and externally scanning the patient for localization of the label.

As described above, the anti-TAT antibodies, oligopeptides and organic molecules of the invention have various non-therapeutic applications. The anti-TAT antibodies, oligopeptides and organic molecules of the present invention can be useful for diagnosis and staging of TAT polypeptide-expressing cancers (e.g., in radioimaging). The antibodies, oligopeptides and organic molecules are also useful for purification or immunoprecipitation of TAT polypeptide from cells, for detection and quantitation of TAT polypeptide *in vitro*, e.g., in an ELISA or a Western blot, to kill and eliminate TAT-expressing cells from a population of mixed cells as a step in the purification of other cells.

Currently, depending on the stage of the cancer, cancer treatment involves one or a combination of the following therapies: surgery to remove the cancerous tissue, radiation therapy, and chemotherapy. Anti-TAT antibody, oligopeptide or organic molecule therapy may be especially desirable in elderly patients who do not tolerate the toxicity and side effects of chemotherapy well and in metastatic disease where radiation therapy has limited usefulness. The tumor targeting anti-TAT antibodies, oligopeptides and organic molecules of the invention are useful to alleviate TAT-expressing cancers upon initial diagnosis of the disease or during relapse. For therapeutic applications, the anti-TAT antibody, oligopeptide or organic molecule can be used alone, or in combination therapy with, e.g., hormones, antimitogens, or radiolabelled compounds, or with surgery, cryotherapy, and/or radiotherapy. Anti-TAT antibody, oligopeptide or organic molecule treatment can be administered in conjunction with other forms of conventional therapy, either consecutively with, pre- or post-conventional therapy. Chemotherapeutic drugs such as TAXOTERE® (docetaxel), TAXOL® (paclitaxel), estramustine and mitoxantrone are used in treating cancer, in particular, in good risk patients. In the present method of the invention for treating or alleviating cancer, the cancer patient can be administered anti-TAT antibody, oligopeptide or organic molecule in conjuction with treatment with the one or more of the preceding chemotherapeutic agents. In particular, combination therapy with paclitaxel and modified derivatives (see, e.g., EP0600517) is contemplated. The anti-TAT antibody, oligopeptide or organic molecule will be administered with a therapeutically effective dose of the chemotherapeutic agent. In another embodiment, the anti-TAT antibody, oligopeptide or organic molecule is administered in conjunction with chemotherapy to enhance the activity and efficacy of the chemotherapeutic agent, e.g., paclitaxel. The Physicians' Desk Reference (PDR) discloses dosages of these agents that have been used in treatment of various cancers. The dosing regimen and dosages of these aforementioned chemotherapeutic drugs that are therapeutically effective will depend on the particular cancer being treated, the extent of the disease and other factors familiar to the physician of skill in the art and can be determined by the physician.

In one particular embodiment, a conjugate comprising an anti-TAT antibody, oligopeptide or organic molecule conjugated with a cytotoxic agent is administered to the patient. Preferably, the immunoconjugate bound to the TAT protein is internalized by the cell, resulting in increased therapeutic efficacy of the immunoconjugate in killing the cancer cell to which it binds. In a preferred embodiment, the cytotoxic agent

targets or interferes with the nucleic acid in the cancer cell. Examples of such cytotoxic agents are described above and include maytansinoids, calicheamicins, ribonucleases and DNA endonucleases.

The anti-TAT antibodies, oligopeptides, organic molecules or toxin conjugates thereof are administered to a human patient, in accord with known methods, such as intravenous administration, e.g., as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. Intravenous or subcutaneous administration of the antibody, oligopeptide or organic molecule is preferred.

Other therapeutic regimens may be combined with the administration of the anti-TAT antibody, oligopeptide or organic molecule. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Preferably such combined therapy results in a synergistic therapeutic effect.

It may also be desirable to combine administration of the anti-TAT antibody or antibodies, oligopeptides or organic molecules, with administration of an antibody directed against another tumor antigen associated with the particular cancer.

In another embodiment, the therapeutic treatment methods of the present invention involves the combined administration of an anti-TAT antibody (or antibodies), oligopeptides or organic molecules and one or more chemotherapeutic agents or growth inhibitory agents, including co-administration of cocktails of different chemotherapeutic agents. Chemotherapeutic agents include estramustine phosphate, prednimustine, cisplatin, 5-fluorouracil, melphalan, cyclophosphamide, hydroxyurea and hydroxyureataxanes (such as paclitaxel and doxetaxel) and/or anthracycline antibiotics. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in Chemotherapy Service Ed., M.C. Perry, Williams & Wilkins, Baltimore, MD (1992).

The antibody, oligopeptide or organic molecule may be combined with an anti-hormonal compound; e.g., an anti-estrogen compound such as tamoxifen; an anti-progesterone such as onapristone (see, EP 616 812); or an anti-androgen such as flutamide, in dosages known for such molecules. Where the cancer to be treated is androgen independent cancer, the patient may previously have been subjected to anti-androgen therapy and, after the cancer becomes androgen independent, the anti-TAT antibody, oligopeptide or organic molecule (and optionally other agents as described herein) may be administered to the patient.

Sometimes, it may be beneficial to also co-administer a cardioprotectant (to prevent or reduce myocardial dysfunction associated with the therapy) or one or more cytokines to the patient. In addition to the above therapeutic regimes, the patient may be subjected to surgical removal of cancer cells and/or radiation therapy, before, simultaneously with, or post antibody, oligopeptide or organic molecule therapy. Suitable dosages for any of the above co-administered agents are those presently used and may be lowered due to the combined action (synergy) of the agent and anti-TAT antibody, oligopeptide or organic molecule.

For the prevention or treatment of disease, the dosage and mode of administration will be chosen by the physician according to known criteria. The appropriate dosage of antibody, oligopeptide or organic

molecule will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the antibody, oligopeptide or organic molecule is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, oligopeptide or organic molecule, and the discretion of the attending physician. The antibody, oligopeptide or organic molecule is suitably administered to the patient at one time or over a series of treatments. Preferably, the antibody, oligopeptide or organic molecule is administered by intravenous infusion or by subcutaneous injections. Depending on the type and severity of the disease, about 1 μg/kg to about 50 mg/kg body weight (e.g., about 0.1-15mg/kg/dose) of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A dosing regimen can comprise administering an initial loading dose of about 4 mg/kg, followed by a weekly maintenance dose of about 2 mg/kg of the anti-TAT antibody. However, other dosage regimens may be useful. A typical daily dosage might range from about 1 μg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. The progress of this therapy can be readily monitored by conventional methods and assays and based on criteria known to the physician or other persons of skill in the art.

Aside from administration of the antibody protein to the patient, the present application contemplates administration of the antibody by gene therapy. Such administration of nucleic acid encoding the antibody is encompassed by the expression "administering a therapeutically effective amount of an antibody". See, for example, WO96/07321 published March 14, 1996 concerning the use of gene therapy to generate intracellular antibodies.

There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells; *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient, usually at the site where the antibody is required. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes which are implanted into the patient (see, e.g., U.S. Patent Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. A commonly used vector for *ex vivo* delivery of the gene is a retroviral vector.

The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral vectors (such as adenovirus, Herpes simplex I virus, or adeno-associated virus) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are DOTMA, DOPE and DC-Chol, for example). For review of the currently known gene marking and gene therapy protocols see Anderson et al., Science 256:808-813 (1992). See also WO 93/25673 and the references cited therein.

The anti-TAT antibodies of the invention can be in the different forms encompassed by the definition of "antibody" herein. Thus, the antibodies include full length or intact antibody, antibody fragments, native sequence antibody or amino acid variants, humanized, chimeric or fusion antibodies, immunoconjugates, and functional fragments thereof. In fusion antibodies an antibody sequence is fused to a heterologous polypeptide sequence. The antibodies can be modified in the Fc region to provide desired effector functions. As discussed in more detail in the sections herein, with the appropriate Fc regions, the naked antibody bound on the cell surface can induce cytotoxicity, e.g., via antibody-dependent cellular cytotoxicity (ADCC) or by recruiting complement in complement dependent cytotoxicity, or some other mechanism. Alternatively, where it is desirable to eliminate or reduce effector function, so as to minimize side effects or therapeutic complications, certain other Fc regions may be used.

In one embodiment, the antibody competes for binding or bind substantially to, the same epitope as the antibodies of the invention. Antibodies having the biological characteristics of the present anti-TAT antibodies of the invention are also contemplated, specifically including the *in vivo* tumor targeting and any cell proliferation inhibition or cytotoxic characteristics.

Methods of producing the above antibodies are described in detail herein.

The present anti-TAT antibodies, oligopeptides and organic molecules are useful for treating a TAT-expressing cancer or alleviating one or more symptoms of the cancer in a mammal. Such a cancer includes prostate cancer, cancer of the urinary tract, lung cancer, breast cancer, colon cancer and ovarian cancer, more specifically, prostate adenocarcinoma, renal cell carcinomas, colorectal adenocarcinomas, lung adenocarcinomas, lung squamous cell carcinomas, and pleural mesothelioma. The cancers encompass metastatic cancers of any of the preceding. The antibody, oligopeptide or organic molecule is able to bind to at least a portion of the cancer cells that express TAT polypeptide in the mammal. In a preferred embodiment, the antibody, oligopeptide or organic molecule is effective to destroy or kill TAT-expressing tumor cells or inhibit the growth of such tumor cells, *in vitro* or *in vivo*, upon binding to TAT polypeptide on the cell. Such an antibody includes a naked anti-TAT antibody (not conjugated to any agent). Naked antibodies that have cytotoxic or cell growth inhibition properties can be further harnessed with a cytotoxic agent to render them even more potent in tumor cell destruction. Cytotoxic properties can be conferred to an anti-TAT antibody by, e.g., conjugating the antibody with a cytotoxic agent, to form an immunoconjugate as described herein. The cytotoxic agent or a growth inhibitory agent is preferably a small molecule. Toxins such as calicheamicin or a maytansinoid and analogs or derivatives thereof, are preferable.

The invention provides a composition comprising an anti-TAT antibody, oligopeptide or organic molecule of the invention, and a carrier. For the purposes of treating cancer, compositions can be administered to the patient in need of such treatment, wherein the composition can comprise one or more anti-TAT antibodies present as an immunoconjugate or as the naked antibody. In a further embodiment, the compositions can comprise these antibodies, oligopeptides or organic molecules in combination with other therapeutic agents such as cytotoxic or growth inhibitory agents, including chemotherapeutic agents. The invention also provides formulations comprising an anti-TAT antibody, oligopeptide or organic molecule of the invention, and a carrier. In one embodiment, the formulation is a therapeutic formulation comprising a pharmaceutically

acceptable carrier.

Another aspect of the invention is isolated nucleic acids encoding the anti-TAT antibodies. Nucleic acids encoding both the H and L chains and especially the hypervariable region residues, chains which encode the native sequence antibody as well as variants, modifications and humanized versions of the antibody, are encompassed.

The invention also provides methods useful for treating a TAT polypeptide-expressing cancer or alleviating one or more symptoms of the cancer in a mammal, comprising administering a therapeutically effective amount of an anti-TAT antibody, oligopeptide or organic molecule to the mammal. The antibody, oligopeptide or organic molecule therapeutic compositions can be administered short term (acute) or chronic, or intermittent as directed by physician. Also provided are methods of inhibiting the growth of, and killing a TAT polypeptide-expressing cell.

The invention also provides kits and articles of manufacture comprising at least one anti-TAT antibody, oligopeptide or organic molecule. Kits containing anti-TAT antibodies, oligopeptides or organic molecules find use, e.g., for TAT cell killing assays, for purification or immunoprecipitation of TAT polypeptide from cells. For example, for isolation and purification of TAT, the kit can contain an anti-TAT antibody, oligopeptide or organic molecule coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies, oligopeptides or organic molecules for detection and quantitation of TAT *in vitro*, e.g., in an ELISA or a Western blot. Such antibody, oligopeptide or organic molecule useful for detection may be provided with a label such as a fluorescent or radiolabel.

I. Articles of Manufacture and Kits

Another embodiment of the invention is an article of manufacture containing materials useful for the treatment of anti-TAT expressing cancer. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the cancer condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-TAT antibody, oligopeptide or organic molecule of the invention. The label or package insert indicates that the composition is used for treating cancer. The label or package insert will further comprise instructions for administering the antibody, oligopeptide or organic molecule composition to the cancer patient. Additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

Kits are also provided that are useful for various purposes , e.g., for TAT-expressing cell killing assays, for purification or immunoprecipitation of TAT polypeptide from cells. For isolation and purification of TAT polypeptide, the kit can contain an anti-TAT antibody, oligopeptide or organic molecule coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies, oligopeptides or organic

molecules for detection and quantitation of TAT polypeptide *in vitro*, e.g., in an ELISA or a Western blot. As with the article of manufacture, the kit comprises a container and a label or package insert on or associated with the container. The container holds a composition comprising at least one anti-TAT antibody, oligopeptide or organic molecule of the invention. Additional containers may be included that contain, e.g., diluents and buffers, control antibodies. The label or package insert may provide a description of the composition as well as instructions for the intended in vitro or diagnostic use.

M. Uses for TAT Polypeptides and TAT-Polypeptide Encoding Nucleic Acids

Nucleotide sequences (or their complement) encoding TAT polypeptides have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA probes. TAT-encoding nucleic acid will also be useful for the preparation of TAT polypeptides by the recombinant techniques described herein, wherein those TAT polypeptides may find use, for example, in the preparation of anti-TAT antibodies as described herein.

The full-length native sequence TAT gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length TAT cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of TAT or TAT from other species) which have a desired sequence identity to the native TAT sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence TAT. By way of example, a screening method will comprise isolating the coding region of the TAT gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as ^{32}P or ^{35}S, or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the TAT gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below. Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

Other useful fragments of the TAT-encoding nucleic acids include antisense or sense oligonucleotides comprising a singe-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target TAT mRNA (sense) or TAT DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of TAT DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means.

Such methods are encompassed by the present invention. The antisense oligonucleotides thus may be used to block expression of TAT proteins, wherein those TAT proteins may play a role in the induction of cancer in mammals. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Preferred intragenic sites for antisense binding include the region incorporating the translation initiation/start codon (5'-AUG / 5'-ATG) or termination/stop codon (5'-UAA, 5'-UAG and 5-UGA / 5'-TAA, 5'-TAG and 5'-TGA) of the open reading frame (ORF) of the gene. These regions refer to a portion of the mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation initiation or termination codon. Other preferred regions for antisense binding include: introns; exons; intron-exon junctions; the open reading frame (ORF) or "coding region," which is the region between the translation initiation codon and the translation termination codon; the 5' cap of an mRNA which comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA via a 5'-5' triphosphate linkage and includes 5' cap structure itself as well as the first 50 nucleotides adjacent to the cap; the 5' untranslated region (5'UTR), the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA or corresponding nucleotides on the gene; and the 3' untranslated region (3'UTR), the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA or corresponding nucleotides on the gene.

Specific examples of preferred antisense compounds useful for inhibiting expression of TAT proteins include oligonucleotides containing modified backbones or non-natural internucleoside linkages. Oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. Preferred modified oligonucleotide backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotri-esters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, selenophosphates and borano-phosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Preferred oligonucleotides having inverted polarity comprise a single 3' to 3' linkage at the 3'-most internucleotide linkage i.e. a single inverted nucleoside residue which may be abasic (the nucleobase is missing or has a hydroxyl group in place thereof). Various salts, mixed salts and free acid forms are also included. Representative United States patents that teach the preparation of phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos.: 3,687,808;

4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,194,599; 5,565,555; 5,527,899; 5,721,218; 5,672,697 and 5,625,050, each of which is herein incorporated by reference.

Preferred modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH.sub.2 component parts. Representative United States patents that teach the preparation of such oligonucleosides include, but are not limited to,. U.S. Pat. Nos.: 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; 5,792,608; 5,646,269 and 5,677,439, each of which is herein incorporated by reference.

In other preferred antisense oligonucleotides, both the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos.: 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al., Science, 1991, 254, 1497-1500.

Preferred antisense oligonucleotides incorporate phosphorothioate backbones and/or heteroatom backbones, and in particular -CH_2-NH-O-CH_2-, -CH_2-N(CH_3)-O-CH_2- [known as a methylene (methylimino) or MMI backbone], -CH_2-O-N(CH_3)-CH_2-, -CH_2-N(CH_3)-N(CH_3)-CH_2- and -O-N(CH_3)-CH_2-CH_2- [wherein the native phosphodiester backbone is represented as -O-P-O-CH_2-] described in the above referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above referenced U.S. Pat. No. 5,602,240. Also preferred are antisense oligonucleotides having morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O-alkyl, S-alkyl, or N-alkyl; O-alkenyl, S-alkenyl, or N-alkenyl; O-alkynyl, S-alkynyl or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl,

alkenyl and alkynyl may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Particularly preferred are $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. Other preferred antisense oligonucleotides comprise one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2 CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O-$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., Helv. Chim. Acta, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-dimethylaminooxyethoxy, i.e., a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH_2-O-CH_2-$N(CH_3)_2$.

A further prefered modification includes Locked Nucleic Acids (LNAs) in which the 2'-hydroxyl group is linked to the 3' or 4' carbon atom of the sugar ring thereby forming a bicyclic sugar moiety. The linkage is preferably a methelyne ($-CH_2-$)$_n$ group bridging the 2' oxygen atom and the 4' carbon atom wherein n is 1 or 2. LNAs and preparation thereof are described in WO 98/39352 and WO 99/14226.

Other preferred modifications include 2'-methoxy (2'-O-CH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$), 2'-allyl (2'-CH_2-CH=CH_2), 2'-O-allyl (2'-O-CH_2-CH=CH_2) and 2'-fluoro (2'-F). The 2'-modification may be in the arabino (up) position or ribo (down) position. A preferred 2'-arabino modification is 2'-F. Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative United States patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos.: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; and 5,700,920, each of which is herein incorporated by reference in its entirety.

Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C$_3$-C$\equiv$C-CH_3 or -CH_2-C$\equiv$CH) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines,

5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further modified nucleobases include tricyclic pyrimidines such as phenoxazine cytidine(1H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine (2H-pyrimido[4,5-b]indol-2-one), pyridoindole cytidine (H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-one). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. I., ed. John Wiley & Sons, 1990, and those disclosed by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi et al, Antisense Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications. Representative United States patents that teach the preparation of modified nucleobases include, but are not limited to: U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos.: 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,645,985; 5,830,653; 5,763,588; 6,005,096; 5,681,941 and 5,750,692, each of which is herein incorporated by reference.

Another modification of antisense oligonucleotides chemically linking to the oligonucleotide one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. The compounds of the invention can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugates groups include cholesterols, lipids, cation lipids, phospholipids, cationic phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve oligomer uptake, enhance oligomer resistance to degradation, and/or strengthen sequence-specific hybridization with RNA. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve oligomer uptake, distribution, metabolism or excretion. Conjugate moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Let., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992,

660, 306-309; Manoharan et al., Bioorg. Med. Chem. Let., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety. Oligonucleotides of the invention may also be conjugated to active drug substances, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic. Oligonucleotide-drug conjugates and their preparation are described in U.S. patent application Ser. No. 09/334,130 (filed Jun. 15, 1999) and United States patents Nos.: 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941, each of which is herein incorporated by reference.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds which are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the oligonucleotide may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide inhibition of gene expression. Consequently, comparable results can often be obtained with shorter oligonucleotides when chimeric oligonucleotides are used, compared to phosphorothioate deoxyoligonucleotides hybridizing to the same target region. Chimeric antisense compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or

oligonucleotide mimetics as described above. Preferred chimeric antisense oligonucleotides incorporate at least one 2' modified sugar (preferably 2'-O-$(CH_2)_2$-O-CH_3) at the 3' terminal to confer nuclease resistance and a region with at least 4 contiguous 2'-H sugars to confer RNase H activity. Such compounds have also been referred to in the art as hybrids or gapmers. Preferred gapmers have a region of 2' modified sugars (preferably 2'-O-$(CH_2)_2$-O-CH_3) at the 3'-terminal and at the 5' terminal separated by at least one region having at least 4 contiguous 2'-H sugars and preferably incorporate phosphorothioate backbone linkages. Representative United States patents that teach the preparation of such hybrid structures include, but are not limited to, U.S. Pat. Nos. 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, each of which is herein incorporated by reference in its entirety.

The antisense compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives. The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption. Representative United States patents that teach the preparation of such uptake, distribution and/or absorption assisting formulations include, but are not limited to, U.S. Pat. Nos. 5,108,921; 5,354,844; 5,416,016; 5,459,127; 5,521,291; 5,543,158; 5,547,932; 5,583,020; 5,591,721; 4,426,330; 4,534,899; 5,013,556; 5,108,921; 5,213,804; 5,227,170; 5,264,221; 5,356,633; 5,395,619; 5,416,016; 5,417,978; 5,462,854; 5,469,854; 5,512,295; 5,527,528; 5,534,259; 5,543,152; 5,556,948; 5,580,575; and 5,595,756, each of which is herein incorporated by reference.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, $CaPO_4$-mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

Antisense or sense RNA or DNA molecules are generally at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related TAT coding sequences.

Nucleotide sequences encoding a TAT can also be used to construct hybridization probes for mapping the gene which encodes that TAT and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequences for TAT encode a protein which binds to another protein (example, where the TAT is a receptor), the TAT can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor TAT can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of a native TAT or a receptor for TAT. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

Nucleic acids which encode TAT or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding TAT can be used to clone genomic DNA encoding TAT in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding TAT. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for TAT transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding TAT introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding TAT. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of TAT can be used to construct a TAT "knock out" animal which has a defective or altered gene encoding TAT as a result of homologous recombination between the endogenous gene encoding TAT and altered genomic DNA encoding TAT introduced into an embryonic stem cell of the animal. For example, cDNA encoding TAT can be used to clone genomic DNA encoding TAT in accordance with established techniques. A portion of the genomic DNA encoding TAT can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, Cell, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., Cell, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the TAT polypeptide.

Nucleic acid encoding the TAT polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective

genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik *et al.*, Proc. Natl. Acad. Sci. USA 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau et al., Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu et al., J. Biol. Chem. 262, 4429-4432 (1987); and Wagner et al., Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson et al., Science 256, 808-813 (1992).

The nucleic acid molecules encoding the TAT polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each TAT nucleic acid molecule of the present invention can be used as a chromosome marker.

The TAT polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the TAT polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. TAT nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

This invention encompasses methods of screening compounds to identify those that mimic the TAT polypeptide (agonists) or prevent the effect of the TAT polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the TAT polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides

with other cellular proteins, including e.g., inhibiting the expression of TAT polypeptide from cells. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a TAT polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the TAT polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the TAT polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the TAT polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular TAT polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β-galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended

to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a TAT polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the TAT polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the TAT polypeptide indicates that the compound is an antagonist to the TAT polypeptide. Alternatively, antagonists may be detected by combining the TAT polypeptide and a potential antagonist with membrane-bound TAT polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The TAT polypeptide can be labeled, such as by radioactivity, such that the number of TAT polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the TAT polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the TAT polypeptide. Transfected cells that are grown on glass slides are exposed to labeled TAT polypeptide. The TAT polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, labeled TAT polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled TAT polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with TAT polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the TAT polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the TAT polypeptide.

Another potential TAT polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature TAT polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the TAT polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the TAT polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the TAT polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the TAT polypeptide, thereby blocking the normal biological activity of the TAT polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

Isolated TAT polypeptide-encoding nucleic acid can be used herein for recombinantly producing TAT polypeptide using techniques well known in the art and as described herein. In turn, the produced TAT polypeptides can be employed for generating anti-TAT antibodies using techniques well known in the art and as described herein.

Antibodies specifically binding a TAT polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders, including cancer, in the form of pharmaceutical compositions.

If the TAT polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, *e.g.*, Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1: Tissue Expression Profiling Using GeneExpress®

A proprietary database containing gene expression information (GeneExpress®, Gene Logic Inc., Gaithersburg, MD) was analyzed in an attempt to identify polypeptides (and their encoding nucleic acids) whose expression is significantly upregulated in a particular tumor tissue(s) of interest as compared to other tumor(s) and/or normal tissues. Specifically, analysis of the GeneExpress® database was conducted using either software available through Gene Logic Inc., Gaithersburg, MD, for use with the GeneExpress® database

or with proprietary software written and developed at Genentech, Inc. for use with the GeneExpress® database. The rating of positive hits in the analysis is based upon several criteria including, for example, tissue specificity, tumor specificity and expression level in normal essential and/or normal proliferating tissues. The following is a list of molecules whose tissue expression profile as determined from an analysis of the GeneExpress® database evidences high tissue expression and significant upregulation of expression in a specific tumor or tumors as compared to other tumor(s) and/or normal tissues and optionally relatively low expression in normal essential and/or normal proliferating tissues. As such, the molecules listed below are excellent polypeptide targets for the diagnosis and therapy of cancer in mammals.

Molecule	upregulation of expression in:	as compared to:
DNA77507 (TAT161)	breast tumor	normal breast tissue
DNA77507 (TAT161)	colon tumor	normal colon tissue
DNA77507 (TAT161)	lung tumor	normal lung tissue
DNA77507 (TAT161)	kidney tumor	normal kidney tissue
DNA77507 (TAT161)	liver tumor	normal liver tissue
DNA77507 (TAT161)	ovarian tumor	normal ovarian tissue
DNA77507 (TAT161)	pancreatic tumor	normal pancreatic tissue
DNA77507 (TAT161)	rectum tumor	normal rectum tissue
DNA77507 (TAT161)	skin tumor	normal skin tissue
DNA77507 (TAT161)	uterine tumor	normal uterine tissue
DNA77507 (TAT161)	brain tumor	normal brain tissue
DNA77507 (TAT161)	soft tissue tumor	normal soft tissue
DNA77507 (TAT161)	bone tumor	normal bone tissue
DNA80894 (TAT101)	breast tumor	normal breast tissue
DNA82343 (TAT157)	colon tumor	normal colon tissue
DNA82343 (TAT157)	ovarian tumor	normal ovarian tissue
DNA82343 (TAT157)	stomach tumor	normal stomach tissue
DNA82343 (TAT157)	liver tumor	normal liver tissue
DNA82343 (TAT157)	rectum tumor	normal rectum tissue
DNA82343 (TAT157)	small intestine tumor	normal small intestine tissue
DNA82343 (TAT157)	esophagus tumor	normal esophagus tissue
DNA82343 (TAT157)	testis tumor	normal testis tissue
DNA82343 (TAT157)	thymus tumor	normal thymus tissue
DNA87994 (TAT160)	breast tumor	normal breast tissue
DNA87994 (TAT160)	pancreatic tumor	normal pancreatic tissue
DNA87994 (TAT160)	rectum tumor	normal rectum tissue
DNA87994 (TAT160)	colon tumor	normal colon tissue
DNA87994 (TAT160)	esophagus tumor	normal esophagus tissue
DNA87994 (TAT160)	ovarian tumor	normal ovarian tissue
DNA87994 (TAT160)	lung tumor	normal lung tissue
DNA87994 (TAT160)	uterine tumor	normal uterine tissue
DNA88131 (TAT158)	bone tumor	normal bone tissue
DNA88131 (TAT158)	breast tumor	normal breast tissue
DNA88131 (TAT158)	colon tumor	normal colon tissue
DNA88131 (TAT158)	uterine tumor	normal uterine tissue
DNA88131 (TAT158)	esophagus tumor	normal esophagus tissue
DNA88131 (TAT158)	lung tumor	normal lung tissue
DNA88131 (TAT158)	ovarian tumor	normal ovarian tissue
DNA88131 (TAT158)	pancreatic tumor	normal pancreatic tissue
DNA88131 (TAT158)	prostate tumor	normal prostate tissue
DNA88131 (TAT158)	skin tumor	normal skin tissue
DNA88131 (TAT158)	soft tissue tumor	normal soft tissue
DNA88131 (TAT158)	stomach tumor	normal stomach tissue

Molecule	upregulation of expression in:	as compared to:
DNA88131 (TAT158)	rectum tumor	normal rectum tissue
DNA88131 (TAT158)	neuroendocrine tumor	normal neuroendocrine tissue
DNA88131 (TAT158)	brain tumor	normal brain tissue
DNA95930 (TAT110)	colon tumor	normal colon tissue
DNA95930 (TAT110)	uterine tumor	normal uterine tissue
DNA95930 (TAT110)	endometrial tumor	normal endometrial tissue
DNA95930 (TAT110)	rectum tumor	normal rectum tissue
DNA95930 (TAT110)	ovarian tumor	normal ovarian tissue
DNA95930 (TAT110)	breast tumor	normal breast tissue
DNA95930 (TAT110)	lung tumor	normal lung tissue
DNA95930 (TAT110)	prostate tumor	normal prostate tissue
DNA95930-1 (TAT210)	colon tumor	normal colon tissue
DNA95930-1 (TAT210)	uterine tumor	normal uterine tissue
DNA95930-1 (TAT210)	endometrial tumor	normal endometrial tissue
DNA95930-1 (TAT210)	rectum tumor	normal rectum tissue
DNA95930-1 (TAT210)	ovarian tumor	normal ovarian tissue
DNA95930-1 (TAT210)	breast tumor	normal breast tissue
DNA95930-1 (TAT210)	lung tumor	normal lung tissue
DNA95930-1 (TAT210)	prostate tumor	normal prostate tissue
DNA96917 (TAT159)	pancreatic tumor	normal pancreatic tissue
DNA96917 (TAT159)	lung tumor	normal lung tissue
DNA96917 (TAT159)	liver tumor	normal liver tissue
DNA96930 (TAT112)	breast tumor	normal breast tissue
DNA96930 (TAT112)	colon tumor	normal colon tissue
DNA96930 (TAT112)	rectum tumor	normal rectum tissue
DNA96930 (TAT112)	uterine tumor	normal uterine tissue
DNA96930 (TAT112)	lung tumor	normal lung tissue
DNA96930 (TAT112)	ovarian tumor	normal ovarian tissue
DNA96930 (TAT112)	pancreatic tumor	normal pancreatic tissue
DNA96930 (TAT112)	stomach tumor	normal stomach tissue
DNA96936 (TAT147)	breast tumor	normal breast tissue
DNA96936 (TAT147)	colon tumor	normal colon tissue
DNA96936 (TAT147)	testis tumor	normal testis tissue
DNA96936 (TAT147)	ovarian tumor	normal ovarian tissue
DNA98565 (TAT145)	brain tumor	normal brain tissue
DNA98565 (TAT145)	glioma	normal glial tissue
DNA246435 (TAT152)	brain tumor	normal brain tissue
DNA246435 (TAT152)	glioma	normal glial tissue
DNA98591 (TAT162)	colon tumor	normal colon tissue
DNA98591 (TAT162)	rectum tumor	normal rectum tissue
DNA98591 (TAT162)	ovarian tumor	normal ovarian tissue
DNA98591 (TAT162)	pancreatic tumor	normal pancreatic tissue
DNA98591 (TAT162)	stomach tumor	normal stomach tissue
DNA108809 (TAT114)	colon tumor	normal colon tissue
DNA108809 (TAT114)	kidney tumor	normal kidney tissue
DNA119488 (TAT119)	colon tumor	normal colon tissue
DNA119488 (TAT119)	lung tumor	normal lung tissue
DNA119488 (TAT119)	rectum tumor	normal rectum tissue
DNA143493 (TAT103)	breast tumor	normal breast tissue
DNA167234 (TAT130)	prostate tumor	normal prostate tissue
DNA235621 (TAT166)	prostate tumor	normal prostate tissue
DNA235621 (TAT166)	liver tumor	normal liver tissue
DNA176766 (TAT132)	kidney tumor	normal kidney tissue
DNA176766 (TAT132)	ovarian tumor	normal ovarian tissue
DNA176766 (TAT132)	uterine tumor	normal uterine tissue

Molecule	upregulation of expression in:	as compared to:
DNA236463 (TAT150)	kidney tumor	normal kidney tissue
DNA236463 (TAT150)	ovarian tumor	normal ovarian tissue
DNA236463 (TAT150)	uterine tumor	normal uterine tissue
DNA181162 (TAT129)	prostate tumor	normal prostate tissue
DNA188221 (TAT111)	colon tumor	normal colon tissue
DNA188221 (TAT111)	endometrial tumor	normal endometrial tissue
DNA188221 (TAT111)	stomach tumor	normal stomach tissue
DNA233876 (TAT146)	colon tumor	normal colon tissue
DNA233876 (TAT146)	endometrial tumor	normal endometrial tissue
DNA233876 (TAT146)	stomach tumor	normal stomach tissue
DNA193891 (TAT148)	colon tumor	normal colon tissue
DNA248170 (TAT187)	colon tumor	normal colon tissue
DNA248170 (TAT187)	breast tumor	normal breast tissue
DNA194628 (TAT118)	kidney tumor	normal kidney tissue
DNA246415 (TAT167)	kidney tumor	normal kidney tissue
DNA215609 (TAT113)	colon tumor	normal colon tissue
DNA215609 (TAT113)	rectum tumor	normal rectum tissue
DNA220432 (TAT128)	prostate tumor	normal prostate tissue
DNA226094 (TAT164)	breast tumor	normal breast tissue
DNA226094 (TAT164)	brain tumor	normal brain tissue
DNA226094 (TAT164)	lung tumor	normal lung tissue
DNA226094 (TAT164)	skin tumor	normal skin tissue
DNA226165 (TAT122)	breast tumor	normal breast tissue
DNA226165 (TAT122)	endometrial tumor	normal endometrial tissue
DNA226165 (TAT122)	kidney tumor	normal kidney tissue
DNA226165 (TAT122)	lung tumor	normal lung tissue
DNA226165 (TAT122)	ovarian tumor	normal ovarian tissue
DNA226165 (TAT122)	colon tumor	normal colon tissue
DNA226165 (TAT122)	rectum tumor	normal rectum tissue
DNA226165 (TAT122)	skin tumor	normal skin tissue
DNA226165 (TAT122)	soft tissue tumor	normal soft tissue tissue
DNA226165 (TAT122)	bladder tumor	normal bladder tissue
DNA226237 (TAT117)	kidney tumor	normal kidney tissue
DNA246450 (TAT168)	kidney tumor	normal kidney tissue
DNA226456 (TAT144)	breast tumor	normal breast tissue
DNA226456 (TAT144)	colon tumor	normal colon tissue
DNA226456 (TAT144)	rectum tumor	normal rectum tissue
DNA226456 (TAT144)	endometrial tumor	normal endometrial tissue
DNA226456 (TAT144)	kidney tumor	normal kidney tissue
DNA226456 (TAT144)	lung tumor	normal lung tissue
DNA226456 (TAT144)	ovarian tumor	normal ovarian tissue
DNA226456 (TAT144)	skin tumor	normal skin tissue
DNA237637 (TAT188)	breast tumor	normal breast tissue
DNA237637 (TAT188)	colon tumor	normal colon tissue
DNA237637 (TAT188)	rectum tumor	normal rectum tissue
DNA237637 (TAT188)	endometrial tumor	normal endometrial tissue
DNA237637 (TAT188)	kidney tumor	normal kidney tissue
DNA237637 (TAT188)	lung tumor	normal lung tissue
DNA237637 (TAT188)	ovarian tumor	normal ovarian tissue
DNA237637 (TAT188)	skin tumor	normal skin tissue
DNA237637 (TAT188)	liver tumor	normal liver tissue
DNA237637 (TAT188)	lung tumor	normal lung tissue
DNA226539 (TAT126)	breast tumor	normal breast tissue
DNA226539 (TAT126)	colon tumor	normal colon tissue
DNA226539 (TAT126)	rectum tumor	normal rectum tissue

Molecule	upregulation of expression in:	as compared to:
DNA226539 (TAT126)	endometrial tumor	normal endometrial tissue
DNA226539 (TAT126)	lung tumor	normal lung tissue
DNA226539 (TAT126)	ovarian tumor	normal ovarian tissue
DNA226539 (TAT126)	pancreatic tumor	normal pancreatic tissue
DNA236511 (TAT151)	breast tumor	normal breast tissue
DNA236511 (TAT151)	colon tumor	normal colon tissue
DNA236511 (TAT151)	rectum tumor	normal rectum tissue
DNA236511 (TAT151)	endometrial tumor	normal endometrial tissue
DNA236511 (TAT151)	lung tumor	normal lung tissue
DNA236511 (TAT151)	ovarian tumor	normal ovarian tissue
DNA236511 (TAT151)	pancreatic tumor	normal pancreatic tissue
DNA226771 (TAT115)	breast tumor	normal breast tissue
DNA226771 (TAT115)	colon tumor	normal colon tissue
DNA227087 (TAT163)	breast tumor	normal breast tissue
DNA227087 (TAT163)	colon tumor	normal colon tissue
DNA227087 (TAT163)	rectum tumor	normal rectum tissue
DNA227087 (TAT163)	lung tumor	normal lung tissue
DNA227087 (TAT163)	ovarian tumor	normal ovarian tissue
DNA227087 (TAT163)	prostate tumor	normal prostate tissue
DNA227087 (TAT163)	endocrine tumor	normal endocrine tissue
DNA227087 (TAT163)	kidney tumor	normal kidney tissue
DNA227087 (TAT163)	liver tumor	normal liver tissue
DNA227087 (TAT163)	nervous system tumor	normal nervous system tissue
DNA227087 (TAT163)	pancreatic tumor	normal pancreatic tissue
DNA227087 (TAT163)	uterine tumor	normal uterine tissue
DNA227087 (TAT163)	small intestine tumor	normal small intestine tissue
DNA227087 (TAT163)	lymphoid tumor	normal lymphoid tissue
DNA266307 (TAT227)	breast tumor	normal breast tissue
DNA266307 (TAT227)	colon tumor	normal colon tissue
DNA266307 (TAT227)	rectum tumor	normal rectum tissue
DNA266307 (TAT227)	lung tumor	normal lung tissue
DNA266307 (TAT227)	ovarian tumor	normal ovarian tissue
DNA266307 (TAT227)	prostate tumor	normal prostate tissue
DNA266307 (TAT227)	endocrine tumor	normal endocrine tissue
DNA266307 (TAT227)	kidney tumor	normal kidney tissue
DNA266307 (TAT227)	liver tumor	normal liver tissue
DNA266307 (TAT227)	nervous system tumor	normal nervous system tissue
DNA266307 (TAT227)	pancreatic tumor	normal pancreatic tissue
DNA266307 (TAT227)	uterine tumor	normal uterine tissue
DNA266307 (TAT227)	small intestine tumor	normal small intestine tissue
DNA266307 (TAT227)	lymphoid tumor	normal lymphoid tissue
DNA266311 (TAT228)	breast tumor	normal breast tissue
DNA266311 (TAT228)	colon tumor	normal colon tissue
DNA266311 (TAT228)	rectum tumor	normal rectum tissue
DNA266311 (TAT228)	lung tumor	normal lung tissue
DNA266311 (TAT228)	ovarian tumor	normal ovarian tissue
DNA266311 (TAT228)	prostate tumor	normal prostate tissue
DNA266311 (TAT228)	endocrine tumor	normal endocrine tissue
DNA266311 (TAT228)	kidney tumor	normal kidney tissue
DNA266311 (TAT228)	liver tumor	normal liver tissue
DNA266311 (TAT228)	nervous system tumor	normal nervous system tissue
DNA266311 (TAT228)	pancreatic tumor	normal pancreatic tissue
DNA266311 (TAT228)	uterine tumor	normal uterine tissue
DNA266311 (TAT228)	small intestine tumor	normal small intestine tissue
DNA266311 (TAT228)	lymphoid tumor	normal lymphoid tissue

Molecule	upregulation of expression in:	as compared to:
DNA266312 (TAT229)	breast tumor	normal breast tissue
DNA266312 (TAT229)	colon tumor	normal colon tissue
DNA266312 (TAT229)	rectum tumor	normal rectum tissue
DNA266312 (TAT229)	lung tumor	normal lung tissue
DNA266312 (TAT229)	ovarian tumor	normal ovarian tissue
DNA266312 (TAT229)	prostate tumor	normal prostate tissue
DNA266312 (TAT229)	endocrine tumor	normal endocrine tissue
DNA266312 (TAT229)	kidney tumor	normal kidney tissue
DNA266312 (TAT229)	liver tumor	normal liver tissue
DNA266312 (TAT229)	nervous system tumor	normal nervous system tissue
DNA266312 (TAT229)	pancreatic tumor	normal pancreatic tissue
DNA266312 (TAT229)	uterine tumor	normal uterine tissue
DNA266312 (TAT229)	small intestine tumor	normal small intestine tissue
DNA266312 (TAT229)	lymphoid tumor	normal lymphoid tissue
DNA266313 (TAT230)	breast tumor	normal breast tissue
DNA266313 (TAT230)	colon tumor	normal colon tissue
DNA266313 (TAT230)	rectum tumor	normal rectum tissue
DNA266313 (TAT230)	lung tumor	normal lung tissue
DNA266313 (TAT230)	ovarian tumor	normal ovarian tissue
DNA266313 (TAT230)	prostate tumor	normal prostate tissue
DNA266313 (TAT230)	endocrine tumor	normal endocrine tissue
DNA266313 (TAT230)	kidney tumor	normal kidney tissue
DNA266313 (TAT230)	liver tumor	normal liver tissue
DNA266313 (TAT230)	nervous system tumor	normal nervous system tissue
DNA266313 (TAT230)	pancreatic tumor	normal pancreatic tissue
DNA266313 (TAT230)	uterine tumor	normal uterine tissue
DNA266313 (TAT230)	small intestine tumor	normal small intestine tissue
DNA266313 (TAT230)	lymphoid tumor	normal lymphoid tissue
DNA227224 (TAT121)	breast tumor	normal breast tissue
DNA227224 (TAT121)	colon tumor	normal colon tissue
DNA227224 (TAT121)	rectum tumor	normal rectum tissue
DNA227224 (TAT121)	endometrial tumor	normal endometrial tissue
DNA227224 (TAT121)	kidney tumor	normal kidney tissue
DNA227224 (TAT121)	lung tumor	normal lung tissue
DNA227224 (TAT121)	ovarian tumor	normal ovarian tissue
DNA227224 (TAT121)	skin tumor	normal skin tissue
DNA227224 (TAT121)	testis tumor	normal testis tissue
DNA227224 (TAT121)	bladder tumor	normal bladder tissue
DNA247486 (TAT183)	breast tumor	normal breast tissue
DNA247486 (TAT183)	colon tumor	normal colon tissue
DNA247486 (TAT183)	rectum tumor	normal rectum tissue
DNA247486 (TAT183)	endometrial tumor	normal endometrial tissue
DNA247486 (TAT183)	kidney tumor	normal kidney tissue
DNA247486 (TAT183)	lung tumor	normal lung tissue
DNA247486 (TAT183)	ovarian tumor	normal ovarian tissue
DNA247486 (TAT183)	skin tumor	normal skin tissue
DNA247486 (TAT183)	testis tumor	normal testis tissue
DNA247486 (TAT183)	bladder tumor	normal bladder tissue
DNA227800 (TAT131)	prostate tumor	normal prostate tissue
DNA228199 (TAT127)	breast tumor	normal breast tissue
DNA228199 (TAT127)	endometrial tumor	normal endometrial tissue
DNA228199 (TAT127)	ovarian tumor	normal ovarian tissue
DNA228199 (TAT127)	pancreatic tumor	normal pancreatic tissue
DNA228199 (TAT127)	lung tumor	normal lung tissue
DNA228201 (TAT116)	colon tumor	normal colon tissue

Molecule	upregulation of expression in:	as compared to:
DNA228201 (TAT116)	rectum tumor	normal rectum tissue
DNA247488 (TAT189)	colon tumor	normal colon tissue
DNA247488 (TAT189)	rectum tumor	normal rectum tissue
DNA236538 (TAT190)	colon tumor	normal colon tissue
DNA236538 (TAT190)	rectum tumor	normal rectum tissue
DNA247489 (TAT191)	colon tumor	normal colon tissue
DNA247489 (TAT191)	rectum tumor	normal rectum tissue
DNA228211 (TAT133)	uterine tumor	normal uterine tissue
DNA233937 (TAT186)	uterine tumor	normal uterine tissue
DNA233937 (TAT186)	ovarian tumor	normal ovarian tissue
DNA228994 (TAT124)	lung tumor	normal lung tissue
DNA228994 (TAT124)	ovarian tumor	normal ovarian tissue
DNA228994 (TAT124)	skin tumor	normal skin tissue
DNA228994 (TAT124)	breast tumor	normal breast tissue
DNA229410 (TAT105)	breast tumor	normal breast tissue
DNA229411 (TAT107)	breast tumor	normal breast tissue
DNA229413 (TAT108)	breast tumor	normal breast tissue
DNA229700 (TAT139)	breast tumor	normal breast tissue
DNA231312 (TAT143)	breast tumor	normal breast tissue
DNA231312 (TAT143)	colon tumor	normal colon tissue
DNA231542 (TAT160)	brain tumor	normal brain tissue
DNA231542 (TAT160)	glioma	normal glial tissue
DNA231542-1 (TAT284)	brain tumor	normal brain tissue
DNA231542-1 (TAT284)	glioma	normal glial tissue
DNA231542-2 (TAT285)	brain tumor	normal brain tissue
DNA231542-2 (TAT285)	glioma	normal glial tissue
DNA297393 (TAT285-1)	brain tumor	normal brain tissue
DNA297393 (TAT285-1)	glioma	normal glial tissue
DNA234833 (TAT149)	colon tumor	normal colon tissue
DNA268022 (TAT231)	colon tumor	normal colon tissue
DNA268022 (TAT231)	breast tumor	normal breast tissue
DNA268022 (TAT231)	ovarian tumor	normal ovarian tissue
DNA236246 (TAT153)	breast tumor	normal breast tissue
DNA236343 (TAT104)	breast tumor	normal breast tissue
DNA236493 (TAT141)	breast tumor	normal breast tissue
DNA236493 (TAT141)	glioblastoma tumor	normal glial tissue
DNA236534 (TAT102)	breast tumor	normal breast tissue
DNA236534 (TAT102)	colon tumor	normal colon tissue
DNA236534 (TAT102)	rectum tumor	normal rectum tissue
DNA236534 (TAT102)	cervical tumor	normal cervical tissue
DNA236534 (TAT102)	endometrial tumor	normal endometrial tissue
DNA236534 (TAT102)	lung tumor	normal lung tissue
DNA236534 (TAT102)	ovarian tumor	normal ovarian tissue
DNA236534 (TAT102)	pancreatic tumor	normal pancreatic tissue
DNA236534 (TAT102)	prostate tumor	normal prostate tissue
DNA236534 (TAT102)	stomach tumor	normal stomach tissue
DNA236534 (TAT102)	bladder tumor	normal bladder tissue
DNA246430 (TAT109)	breast tumor	normal breast tissue
DNA246430 (TAT109)	prostate tumor	normal prostate tissue
DNA247480 (TAT142)	breast tumor	normal breast tissue
DNA247480 (TAT142)	lung tumor	normal lung tissue
DNA264454 (TAT106)	breast tumor	normal breast tissue

EXAMPLE 2: Microarray Analysis to Detect Upregulation of TAT Polypeptides in Cancerous Tumors

Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in diseased tissues as compared to their normal counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes known to be expressed in certain disease states may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (disease tissue) sample is greater than hybridization signal of a probe from a control (normal tissue) sample, the gene or genes overexpressed in the disease tissue are identified. The implication of this result is that an overexpressed protein in a diseased tissue is useful not only as a diagnostic marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition.

The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In one example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in PCT Patent Application Serial No. PCT/US01/10482, filed on March 30, 2001 and which is herein incorporated by reference.

In the present example, cancerous tumors derived from various human tissues were studied for upregulated gene expression relative to cancerous tumors from different tissue types and/or non-cancerous human tissues in an attempt to identify those polypeptides which are overexpressed in a particular cancerous tumor(s). In certain experiments, cancerous human tumor tissue and non-cancerous human tumor tissue of the same tissue type (often from the same patient) were obtained and analyzed for TAT polypeptide expression. Additionally, cancerous human tumor tissue from any of a variety of different human tumors was obtained and compared to a "universal" epithelial control sample which was prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung. mRNA isolated from the pooled tissues represents a mixture of expressed gene products from these different tissues. Microarray hybridization experiments using the pooled control samples generated a linear plot in a 2-color analysis. The slope of the line generated in a 2-color analysis was then used to normalize the ratios of (test:control detection) within each experiment. The normalized ratios from various experiments were then compared and used to identify clustering of gene expression. Thus, the pooled "universal control" sample not only allowed effective relative gene expression determinations in a simple 2-sample comparison, it also allowed multi-sample comparisons across several experiments.

In the present experiments, nucleic acid probes derived from the herein described TAT polypeptide-encoding nucleic acid sequences were used in the creation of the microarray and RNA from various tumor tissues were used for the hybridization thereto. Below is shown the results of these experiments, demonstrating that various TAT polypeptides of the present invention are significantly overexpressed in various human tumor tissues as compared to their normal counterpart tissue(s). Moreover, all of the molecules shown below are significantly overexpressed in their specific tumor tissue(s) as compared to in the "universal" epithelial control.

As described above, these data demonstrate that the TAT polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more cancerous tumors, but also serve as therapeutic targets for the treatment of those tumors.

Molecule	upregulation of expression in:	as compared to:
DNA95930 (TAT110)	colon tumor	normal colon tissue
DNA95930 (TAT110)	lung tumor	normal lung tissue
DNA95930 (TAT110)	prostate tumor	normal prostate tissue
DNA95930 (TAT110)	endometrial tumor	normal endometrial tissue
DNA95930 (TAT110)	ovarian tumor	normal ovarian tissue
DNA95930-1 (TAT210)	colon tumor	normal colon tissue
DNA95930-1 (TAT210)	lung tumor	normal lung tissue
DNA95930-1 (TAT210)	prostate tumor	normal prostate tissue
DNA95930-1 (TAT210)	endometrial tumor	normal endometrial tissue
DNA95930-1 (TAT210)	ovarian tumor	normal ovarian tissue
DNA96930 (TAT112)	colon tumor	normal colon tissue
DNA96930 (TAT112)	breast tumor	normal breast tissue
DNA96930 (TAT112)	lung tumor	normal lung tissue
DNA96936 (TAT147)	breast tumor	normal breast tissue
DNA96936 (TAT147)	colon tumor	normal colon tissue
DNA96936 (TAT147)	ovarian tumor	normal ovarian tissue
DNA96936 (TAT147)	prostate tumor	normal prostate tissue
DNA108809 (TAT114)	colon tumor	normal colon tissue
DNA119488 (TAT119)	colon tumor	normal colon tissue
DNA119488 (TAT119)	lung tumor	normal lung tissue
DNA143493 (TAT103)	breast tumor	normal breast tissue
DNA181162 (TAT129)	prostate tumor	normal prostate tissue
DNA188221 (TAT111)	colon tumor	normal colon tissue
DNA188221 (TAT111)	lung tumor	normal lung tissue
DNA188221 (TAT111)	ovarian tumor	normal ovarian tissue
DNA233876 (TAT146)	colon tumor	normal colon tissue
DNA233876 (TAT146)	lung tumor	normal lung tissue
DNA233876 (TAT146)	ovarian tumor	normal ovarian tissue
DNA210499 (TAT123)	ovarian tumor	normal ovarian tissue
DNA210499 (TAT123)	lung tumor	normal lung tissue
DNA219894 (TAT211)	ovarian tumor	normal ovarian tissue
DNA219894 (TAT211)	lung tumor	normal lung tissue
DNA215609 (TAT113)	colon tumor	normal colon tissue
DNA220432 (TAT128)	prostate tumor	normal prostate tissue
DNA226165 (TAT122)	breast tumor	normal breast tissue
DNA226165 (TAT122)	colon tumor	normal colon tissue
DNA226165 (TAT122)	rectum tumor	normal rectum tissue
DNA226165 (TAT122)	lung tumor	normal lung tissue
DNA226165 (TAT122)	ovarian tumor	normal ovarian tissue
DNA226165 (TAT122)	prostate tumor	normal prostate tissue
DNA226456 (TAT144)	breast tumor	normal breast tissue
DNA226456 (TAT144)	colon tumor	normal colon tissue
DNA237637 (TAT188)	breast tumor	normal breast tissue
DNA237637 (TAT188)	colon tumor	normal colon tissue
DNA226539 (TAT126)	rectum tumor	normal rectum tissue
DNA226539 (TAT126)	colon tumor	normal colon tissue
DNA226539 (TAT126)	lung tumor	normal lung tissue
DNA226539 (TAT126)	ovarian tumor	normal ovarian tissue
DNA236511 (TAT151)	rectum tumor	normal rectum tissue
DNA236511 (TAT151)	colon tumor	normal colon tissue
DNA236511 (TAT151)	lung tumor	normal lung tissue

Molecule	upregulation of expression in:	as compared to:
DNA236511 (TAT151)	ovarian tumor	normal ovarian tissue
DNA226771 (TAT115)	colon tumor	normal colon tissue
DNA227224 (TAT121)	ovarian tumor	normal ovarian tissue
DNA227224 (TAT121)	rectum tumor	normal rectum tissue
DNA227224 (TAT121)	colon tumor	normal colon tissue
DNA227224 (TAT121)	lung tumor	normal lung tissue
DNA227224 (TAT121)	breast tumor	normal breast tissue
DNA227224 (TAT121)	prostate tumor	normal prostate tissue
DNA247486 (TAT183)	ovarian tumor	normal ovarian tissue
DNA247486 (TAT183)	rectum tumor	normal rectum tissue
DNA247486 (TAT183)	colon tumor	normal colon tissue
DNA247486 (TAT183)	lung tumor	normal lung tissue
DNA247486 (TAT183)	breast tumor	normal breast tissue
DNA247486 (TAT183)	prostate tumor	normal prostate tissue
DNA228199 (TAT127)	ovarian tumor	normal ovarian tissue
DNA228199 (TAT127)	lung tumor	normal lung tissue
DNA228201 (TAT116)	colon tumor	normal colon tissue
DNA247488 (TAT189)	colon tumor	normal colon tissue
DNA236538 (TAT190)	colon tumor	normal colon tissue
DNA247489 (TAT191)	colon tumor	normal colon tissue
DNA228094 (TAT124)	lung tumor	normal lung tissue
DNA228994 (TAT124)	breast tumor	normal breast tissue
DNA228994 (TAT124)	ovarian tumor	normal ovarian tissue
DNA231312 (TAT143)	colon tumor	normal colon tissue
DNA231542 (TAT100)	brain tumor	normal brain tissue
DNA231542 (TAT100)	glioma	normal glial tissue
DNA231542-1 (TAT284)	brain tumor	normal brain tissue
DNA231542-1 (TAT284)	glioma	normal glial tissue
DNA231542-2 (TAT285)	brain tumor	normal brain tissue
DNA231542-2 (TAT285)	glioma	normal glial tissue
DNA297393 (TAT285-1)	brain tumor	normal brain tissue
DNA297393 (TAT285-1)	glioma	normal glial tissue
DNA236246 (TAT153)	breast tumor	normal breast tissue
DNA236343 (TAT104)	breast tumor	normal breast tissue
DNA236534 (TAT102)	breast tumor	normal breast tissue
DNA236534 (TAT102)	colon tumor	normal colon tissue
DNA246430 (TAT109)	prostate tumor	normal prostate tissue
DNA264454 (TAT106)	breast tumor	normal breast tissue
DNA98565 (TAT145)	glioma	normal brain tissue
DNA246435 (TAT152)	glioma	normal brain tissue
DNA226094 (TAT164)	glioma	normal brain tissue

EXAMPLE 3: Quantitative Analysis of TAT mRNA Expression

In this assay, a 5' nuclease assay (for example, TaqMan®) and real-time quantitative PCR (for example, ABI Prizm 7700 Sequence Detection System® (Perkin Elmer, Applied Biosystems Division, Foster City, CA)), were used to find genes that are significantly overexpressed in a cancerous tumor or tumors as compared to other cancerous tumors or normal non-cancerous tissue. The 5' nuclease assay reaction is a fluorescent PCR-based technique which makes use of the 5' exonuclease activity of Taq DNA polymerase enzyme to monitor gene expression in real time. Two oligonucleotide primers (whose sequences are based upon the gene or EST sequence of interest) are used to generate an amplicon typical of a PCR reaction. A third oligonucleotide, or probe, is designed to detect nucleotide sequence located between the two PCR

primers. The probe is non-extendible by Taq DNA polymerase enzyme, and is labeled with a reporter fluorescent dye and a quencher fluorescent dye. Any laser-induced emission from the reporter dye is quenched by the quenching dye when the two dyes are located close together as they are on the probe. During the PCR amplification reaction, the Taq DNA polymerase enzyme cleaves the probe in a template-dependent manner. The resultant probe fragments disassociate in solution, and signal from the released reporter dye is free from the quenching effect of the second fluorophore. One molecule of reporter dye is liberated for each new molecule synthesized, and detection of the unquenched reporter dye provides the basis for quantitative interpretation of the data.

The 5' nuclease procedure is run on a real-time quantitative PCR device such as the ABI Prism 7700TM Sequence Detection. The system consists of a thermocycler, laser, charge-coupled device (CCD) camera and computer. The system amplifies samples in a 96-well format on a thermocycler. During amplification, laser-induced fluorescent signal is collected in real-time through fiber optics cables for all 96 wells, and detected at the CCD. The system includes software for running the instrument and for analyzing the data.

The starting material for the screen was mRNA isolated from a variety of different cancerous tissues. The mRNA is quantitated precisely, e.g., fluorometrically. As a negative control, RNA was isolated from various normal tissues of the same tissue type as the cancerous tissues being tested.

5' nuclease assay data are initially expressed as Ct, or the threshold cycle. This is defined as the cycle at which the reporter signal accumulates above the background level of fluorescence. The ΔCt values are used as quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer mRNA results to normal human mRNA results. As one Ct unit corresponds to 1 PCR cycle or approximately a 2-fold relative increase relative to normal, two units corresponds to a 4-fold relative increase, 3 units corresponds to an 8-fold relative increase and so on, one can quantitatively measure the relative fold increase in mRNA expression between two or more different tissues. Using this technique, the molecules listed below have been identified as being significantly overexpressed in a particular tumor(s) as compared to their normal non-cancerous counterpart tissue(s) (from both the same and different tissue donors) and thus, represent excellent polypeptide targets for the diagnosis and therapy of cancer in mammals.

Molecule	upregulation of expression in:	as compared to:
DNA77507 (TAT161)	breast tumor	normal breast tissue
DNA82343 (TAT157)	colon tumor	normal colon tissue
DNA88131 (TAT158)	breast tumor	normal breast tissue
DNA88131 (TAT158)	colon tumor	normal colon tissue
DNA95930 (TAT110)	colon tumor	normal colon tissue
DNA95930 (TAT110)	lung tumor	normal lung tissue
DNA95930 (TAT110)	prostate tumor	normal prostate tissue
DNA95930 (TAT110)	endometrial tumor	normal endometrial tissue
DNA95930 (TAT110)	ovarian tumor	normal ovarian tissue
DNA95930-1 (TAT210)	colon tumor	normal colon tissue
DNA95930-1 (TAT210)	lung tumor	normal lung tissue
DNA95930-1 (TAT210)	prostate tumor	normal prostate tissue
DNA95930-1 (TAT210)	endometrial tumor	normal endometrial tissue

Molecule	upregulation of expression in:	as compared to:
DNA95936-1 (TAT210)	ovarian tumor	normal ovarian tissue
DNA96930 (TAT112)	colon tumor	normal colon tissue
DNA96936 (TAT147)	colon tumor	normal colon tissue
DNA98591 (TAT162)	colon tumor	normal colon tissue
DNA103809 (TAT114)	kidney tumor	normal kidney tissue
DNA119488 (TAT119)	lung tumor	normal lung tissue
DNA188221 (TAT111)	colon tumor	normal colon tissue
DNA233876 (TAT146)	colon tumor	normal colon tissue
DNA193891 (TAT148)	colon tumor	normal colon tissue
DNA248170 (TAT187)	colon tumor	normal colon tissue
DNA194628 (TAT118)	kidney tumor	normal kidney tissue
DNA246415 (TAT167)	kidney tumor	normal kidney tissue
DNA210499 (TAT123)	lung tumor	normal lung tissue
DNA219894 (TAT211)	lung tumor	normal lung tissue
DNA215609 (TAT113)	colon tumor	normal colon tissue
DNA220432 (TAT128)	prostate tumor	normal prostate tissue
DNA226165 (TAT122)	lung tumor	normal lung tissue
DNA226237 (TAT117)	kidney tumor	normal kidney tissue
DNA246450 (TAT168)	kidney tumor	normal kidney tissue
DNA226456 (TAT144)	breast tumor	normal breast tissue
DNA237637 (TAT188)	breast tumor	normal breast tissue
DNA226539 (TAT126)	ovarian tumor	normal ovarian tissue
DNA236511 (TAT151)	ovarian tumor	normal ovarian tissue
DNA227224 (TAT121)	lung tumor	normal lung tissue
DNA247486 (TAT183)	lung tumor	normal lung tissue
DNA227800 (TAT131)	prostate tumor	normal prostate tissue
DNA228199 (TAT127)	ovarian tumor	normal ovarian tissue
DNA228199 (TAT127)	lung tumor	normal lung tissue
DNA228201 (TAT116)	colon tumor	normal colon tissue
DNA247488 (TAT189)	colon tumor	normal colon tissue
DNA236538 (TAT190)	colon tumor	normal colon tissue
DNA247489 (TAT191)	colon tumor	normal colon tissue
DNA228993 (TAT120)	lung tumor	normal lung tissue
DNA228994 (TAT124)	lung tumor	normal lung tissue
DNA236343 (TAT104)	breast tumor	normal breast tissue
DNA236534 (TAT102)	ovarian tumor	normal ovarian tissue
DNA246430 (TAT109)	breast tumor	normal breast tissue
DNA247480 (TAT142)	lung tumor	normal lung tissue
DNA98565 (TAT145)	glioma	normal brain tissue
DNA246435 (TAT152)	glioma	normal brain tissue
DNA226094 (TAT164)	glioma	normal brain tissue
DNA227578 (TAT165)	glioma	normal brain tissue
DNA231542 (TAT100)	glioma	normal brain tissue
DNA231542-1 (TAT284)	glioma	normal brain tissue
DNA231542-2 (TAT285)	glioma	normal brain tissue
DNA297393 (TAT285-1)	glioma	normal brain tissue

EXAMPLE 4: *In situ* Hybridization

In situ hybridization is a powerful and versatile technique for the detection and localization of nucleic acid sequences within cell or tissue preparations. It may be useful, for example, to identify sites of gene expression, analyze the tissue distribution of transcription, identify and localize viral infection, follow changes in specific mRNA synthesis and aid in chromosome mapping.

In situ hybridization was performed following an optimized version of the protocol by Lu and Gillett, Cell Vision 1:169-176 (1994), using PCR-generated ^{33}P-labeled riboprobes. Briefly, formalin-fixed, paraffin-embedded human tissues were sectioned, deparaffinized, deproteinated in proteinase K (20 g/ml) for 15 minutes at 37°C, and further processed for *in situ* hybridization as described by Lu and Gillett, *supra*. A [^{33}-P] UTP-labeled antisense riboprobe was generated from a PCR product and hybridized at 55°C overnight. The slides were dipped in Kodak NTB2 nuclear track emulsion and exposed for 4 weeks.

^{33}P-Riboprobe synthesis:

6.0 μl (125 mCi) of ^{33}P-UTP (Amersham BF 1002, SA < 2000 Ci/mmol) were speed vac dried. To each tube containing dried ^{33}P-UTP, the following ingredients were added:

2.0 μl 5x transcription buffer

1.0 μl DTT (100 mM)

2.0 μl NTP mix (2.5 mM : 10 μ; each of 10 mM GTP, CTP & ATP + 10 μl H_2O)

1.0 μl UTP (50 μM)

1.0 μl Rnasin

1.0 μl DNA template (1μg)

1.0 μl H_2O

1.0 μl RNA polymerase (for PCR products T3 = AS, T7 = S, usually)

The tubes were incubated at 37°C for one hour. 1.0 μl RQ1 DNase were added, followed by incubation at 37°C for 15 minutes. 90 μl TE (10 mM Tris pH 7.6/1 mM EDTA pH 8.0) were added, and the mixture was pipetted onto DE81 paper. The remaining solution was loaded in a Microcon-50 ultrafiltration unit, and spun using program 10 (6 minutes). The filtration unit was inverted over a second tube and spun using program 2 (3 minutes). After the final recovery spin, 100 μl TE were added. 1 μl of the final product was pipetted on DE81 paper and counted in 6 ml of Biofluor II.

The probe was run on a TBE/urea gel. 1-3 μl of the probe or 5 μl of RNA Mrk III were added to 3 μl of loading buffer. After heating on a 95°C heat block for three minutes, the probe was immediately placed on ice. The wells of gel were flushed, the sample loaded, and run at 180-250 volts for 45 minutes. The gel was wrapped in saran wrap and exposed to XAR film with an intensifying screen in -70°C freezer one hour to overnight.

^{33}P-Hybridization

A. Pretreatment of frozen sections

The slides were removed from the freezer, placed on aluminium trays and thawed at room temperature for 5 minutes. The trays were placed in 55°C incubator for five minutes to reduce condensation. The slides were fixed for 10 minutes in 4% paraformaldehyde on ice in the fume hood, and washed in 0.5 x SSC for 5 minutes, at room temperature (25 ml 20 x SSC + 975 ml SQ H_2O). After deproteination in 0.5 μg/ml proteinase K for 10 minutes at 37°C (12.5 μl of 10 mg/ml stock in 250 ml prewarmed RNase-free RNAse buffer), the sections were washed in 0.5 x SSC for 10 minutes at room temperature. The sections were dehydrated in 70%, 95%, 100% ethanol, 2 minutes each.

B. Pretreatment of paraffin-embedded sections

The slides were deparaffinized, placed in SQ H_2O, and rinsed twice in 2 x SSC at room temperature, for 5 minutes each time. The sections were deproteinated in 20 μg/ml proteinase K (500 μl of 10 mg/ml in 250 ml RNase-free RNase buffer; 37°C, 15 minutes) - human embryo, or 8 x proteinase K (100 μl in 250 ml Rnase buffer, 37°C, 30 minutes) - formalin tissues. Subsequent rinsing in 0.5 x SSC and dehydration were performed as described above.

C. Prehybridization

The slides were laid out in a plastic box lined with Box buffer (4 x SSC, 50% formamide) - saturated filter paper.

D. Hybridization

1.0×10^6 cpm probe and 1.0 μl tRNA (50 mg/ml stock) per slide were heated at 95°C for 3 minutes. The slides were cooled on ice, and 48 μl hybridization buffer were added per slide. After vortexing, 50 μl ^{33}P mix were added to 50 μl prehybridization on slide. The slides were incubated overnight at 55°C.

E. Washes

Washing was done 2 x 10 minutes with 2xSSC, EDTA at room temperature (400 ml 20 x SSC + 16 ml 0.25M EDTA, V_f=4L), followed by RNaseA treatment at 37°C for 30 minutes (500 μl of 10 mg/ml in 250 ml Rnase buffer = 20 μg/ml). The slides were washed 2 x 10 minutes with 2 x SSC, EDTA at room temperature. The stringency wash conditions were as follows: 2 hours at 55°C, 0.1 x SSC, EDTA (20 ml 20 x SSC + 16 ml EDTA, V_f=4L).

F. Oligonucleotides

In situ analysis was performed on a variety of DNA sequences disclosed herein. The oligonucleotides employed for these analyses were obtained so as to be complementary to the nucleic acids (or the complements thereof) as shown in the accompanying figures.

G. Results

In situ analysis was performed on a variety of DNA sequences disclosed herein. The results from these analyses are as follows.

(1) DNA95930 (TAT110)

In one analysis, significant expression is observed in 3/3 lung tumors, 3/3 colorectal adenocarcinomas, 1/1 prostate cancers, 3/3 transitional cell carcinomas and 3/3 endometrial adenocarcinomas, wherein the level of expression in the counterpart normal tissues is significantly less.

In a second independent analysis, significant expression is observed in 7/7 endometrial and 12/15 ovarian adenocarcinomas, wherein the level of expression in the counterpart normal tissues is significantly less.

In a third independent analysis, significant expression is observed in 24/26 colorectal tumor samples, wherein the level of expression in the counterpart normal tissue is significantly less.

Finally, in a fourth independent analysis, expression is observed in 8/26 samples of non-malignant prostate tissue, 55/82 samples of primary prostate cancer and in 5/23 samples of metastatic prostate cancer.

(2) DNA95930-1 (TAT210)

In one analysis, significant expression is observed in 3/3 lung tumors, 3/3 colorectal adenocarcinomas, 1/1 prostate cancers, 3/3 transitional cell carcinomas and 3/3 endometrial adenocarcinomas, wherein the level of expression in the counterpart normal tissues is significantly less.

In a second independent analysis, significant expression is observed in 7/7 endometrial and 12/15 ovarian adenocarcinomas, wherein the level of expression in the counterpart normal tissues is significantly less.

In a third independent analysis, significant expression is observed in 24/26 colorectal tumor samples, wherein the level of expression in the counterpart normal tissue is significantly less.

Finally, in a fourth independent analysis, expression is observed in 8/26 samples of non-malignant prostate tissue, 55/82 samples of primary prostate cancer and in 5/23 samples of metastatic prostate cancer.

(3) DNA96930 (TAT112)

Strong expression in colorectal cancers. Expression in the malignant epithelium appears significantly stronger than in adjacent benign epithelium. Additionally, strong expression is observed in all 23 of 23 samples of pancreatic adenocarcinoma tested, wherein expression in normal pancreatic tissue is not detectable.

(4) DNA96936 (TAT147)

In one analysis, a strongly positive signal was observed in 6/6 breast tumors. In another independent analysis, a positive signal was observed in 4/4 non small cell lung carcinomas, wherein the tumors appear to have stronger expression compared with normal lung. 1/1 endometrial adenocarcinomas shows strong expression and 3/3 colorectal adenocarcinomas show variable expression.

(5) DNA108809 (TAT114)

Positive signal in all renal cell carcinomas tested (n=3) while no expression observed in normal kidney tissue. Additionally, positive expression is observed in 5/12 stomach tumors, 5/24 colorectal tumors, 3/8 pancreatic tumors and 1/3 lung tumors. Normal non-cancerous tissue expression is limited to stomach and small intestine.

(6) DNA176766 (TAT132)

Positive signal in all endometrial adenocarcinomas tested (n=3) while no expression observed in normal endometrial tissue.

(7) DNA236463 (TAT150)

Positive signal in all endometrial adenocarcinomas tested (n=3) while no expression observed in normal endometrial tissue.

(8) DNA181162 (TAT129)

Neoplastic prostate epithelia are generally positive, with signal intensities varying from weak to strong between cases. Non-prostatic tissues are negative.

(9) DNA188221 (TAT111)

Strong signal seen in colonic multi-tumor array over malignant epithelium. In normal tissues, a certain probe gave specific signal over epithelial cells lining the lower 2/3 of the colonic crypts, the intensity of signal appeared significantly lower than in the colonic carcinomas. Positive expression is observed in 12/18 colorectal adenocarcinomas, 6/8 metastatic adenocarcinomas and 2/9 gastric adenocarcinomas.

(10) DNA253876 (TAT146)

Strong signal seen in colonic multi-tumor array over malignant epithelium. In normal tissues, a certain probe gave specific signal over epithelial cells lining the lower 2/3 of the colonic crypts, the intensity of signal appeared significantly lower than in the colonic carcinomas. Positive expression is observed in 12/18 colorectal adenocarcinomas, 6/8 metastatic adenocarcinomas and 2/9 gastric adenocarcinomas.

(11) DNA210499 (TAT123)

In one analysis, 12/14 ovarian adenocarcinomas are positive and 8/9 endometrial adenocarcinomas are positive. Normal ovarian stroma is negative as is uterine myometrium. Other normal ovarian and uterine tissues are negative.

In an independent analysis, 16/27 non small cell lung carcinomas are positive, wherein the signal is moderate or strong.

(12) DNA219894 (TAT211)

In one analysis, 12/14 ovarian adenocarcinomas are positive and 8/9 endometrial adenocarcinomas are positive. Normal ovarian stroma is negative as is uterine myometrium. Other normal ovarian and uterine tissues are negative.

In an independent analysis, 16/27 non small cell lung carcinomas are positive, wherein the signal is moderate or strong.

(13) DNA215609 (TAT113)

Strong signal seen in colonic carcinomas, with only very low level signal in normal colon. Lung and breast carcinomas were negative.

(14) DNA220432 (TAT128)

The only normal adult tissue expressing this gene is prostatic epithelium. The expression is of moderate to strong intensity and focal, it is more prevalent in hyperplastic epithelium.

In one analysis where 50 cases of primary prostate cancer are available for review, 29 cases (58%) are positive, 18 cases (36%) are negative and 3 cases (6%) are equivocal. In another analysis where 37 cases of primary prostate cancer are available for review, 33 cases (89%) are positive, 4 cases (11%) are negative. Finally, in another independent analysis where 27 cases of metastatic prostate cancer are available for review, 14 cases (52%) are positive, 11 cases (41%) are negative and 2 cases (7%) are equivocal.

(15) DNA226237 (TAT117)

In one analysis, two of 3 renal cell carcinomas are positive, wherein normal kidney expression is negative.

(16) DNA246450 (TAT168)

In one analysis, two of 3 renal cell carcinomas are positive, wherein normal kidney expression is negative.

(17) DNA227087 (TAT163)

A probe for this molecule showed a positive signal in a subpopulation of tumor-associated stromal cells in all tested cases of lung, breast, colon, pancreatic and endometrial carcinomas. The intensity of the labeling was often quite strong. In a case of colon adenocarcinoma with adjacent benign colon, labeling was

restricted to the tumor-associated stroma and the normal benign tissue was negative. A breast fibroadenoma also showed labeling of subepithelial stromal cells.

(18) DNA266307 (TAT227)

A probe for this molecule showed a positive signal in a subpopulation of tumor-associated stromal cells in all tested cases of lung, breast, colon, pancreatic and endometrial carcinomas. The intensity of the labeling was often quite strong. In a case of colon adenocarcinoma with adjacent benign colon, labeling was restricted to the tumor-associated stroma and the normal benign tissue was negative. A breast fibroadenoma also showed labeling of subepithelial stromal cells.

(19) DNA266311 (TAT228)

A probe for this molecule showed a positive signal in a subpopulation of tumor-associated stromal cells in all tested cases of lung, breast, colon, pancreatic and endometrial carcinomas. The intensity of the labeling was often quite strong. In a case of colon adenocarcinoma with adjacent benign colon, labeling was restricted to the tumor-associated stroma and the normal benign tissue was negative. A breast fibroadenoma also showed labeling of subepithelial stromal cells.

(20) DNA266312 (TAT229)

A probe for this molecule showed a positive signal in a subpopulation of tumor-associated stromal cells in all tested cases of lung, breast, colon, pancreatic and endometrial carcinomas. The intensity of the labeling was often quite strong. In a case of colon adenocarcinoma with adjacent benign colon, labeling was restricted to the tumor-associated stroma and the normal benign tissue was negative. A breast fibroadenoma also showed labeling of subepithelial stromal cells.

(21) DNA266313 (TAT230)

A probe for this molecule showed a positive signal in a subpopulation of tumor-associated stromal cells in all tested cases of lung, breast, colon, pancreatic and endometrial carcinomas. The intensity of the labeling was often quite strong. In a case of colon adenocarcinoma with adjacent benign colon, labeling was restricted to the tumor-associated stroma and the normal benign tissue was negative. A breast fibroadenoma also showed labeling of subepithelial stromal cells.

(22) DNA227224 (TAT121)

Expression is seen in 2 of 3 endometrial adenocarcinomas.

(23) DNA247486 (TAT183)

Expression is seen in 2 of 3 endometrial adenocarcinomas.

(24) DNA227800 (TAT131)

In one analysis, 46/64 primary prostate cancers are positive and 6/14 metastatic prostate cancers are positive. Weak to moderate expression is seen in prostate epithelium

(25) DNA228199 (TAT127)

Expression is observed in 13 of 15 ovarian tumors (adenocarcinoma and surface epithelial tumors). Benign ovarian surface epithelium is also positive. The expression level in most positive tumors is strong or moderate and fairly uniform. Expression is also observed in 8 of 9 uterine adenocarcinomas. Seven of 23 non small cell lung carcinomas are positive.

(26) DNA228201 (TAT116)

The malignant cells of 13/16 colorectal adenocarcinomas are positive for TAT116 expression. Additionally, 9/10 metastatic adenocarcinomas are positive for expression. Expression is also observed in the basal portions of normal colonic crypts.

(27) DNA247488 (TAT189)

The malignant cells of 13/16 colorectal adenocarcinomas are positive for TAT189 expression. Additionally, 9/10 metastatic adenocarcinomas are positive for expression. Expression is also observed in the basal portions of normal colonic crypts.

(28) DNA236538 (TAT190)

The malignant cells of 13/16 colorectal adenocarcinomas are positive for TAT190 expression. Additionally, 9/10 metastatic adenocarcinomas are positive for expression. Expression is also observed in the basal portions of normal colonic crypts.

(29) DNA247489 (TAT191)

The malignant cells of 13/16 colorectal adenocarcinomas are positive for TAT191 expression. Additionally, 9/10 metastatic adenocarcinomas are positive for expression. Expression is also observed in the basal portions of normal colonic crypts.

(30) DNA228994 (TAT124)

Thirteen of 61 cass of non small cell lung carcinoma are positive for expression of TAT124. Expression level in these positive tumor samples is significantly higher than in normal adult tissues.

(31) DNA231542 (TAT100)

In situ analysis performed as described above evidences significantly upregulated expression in human glioma and glioblastoma tissues as compared to normal brain (and other) tissue.

(32) DNA231542-1 (TAT284)

In situ analysis performed as described above evidences significantly upregulated expression in human glioma and glioblastoma tissues as compared to normal brain (and other) tissue.

(33) DNA231542-2 (TAT285)

In situ analysis performed as described above evidences significantly upregulated expression in human glioma and glioblastoma tissues as compared to normal brain (and other) tissue.

(34) DNA297393 (TAT285-1)

In situ analysis performed as described above evidences significantly upregulated expression in human glioma and glioblastoma tissues as compared to normal brain (and other) tissue.

(35) DNA236534 (TAT102)

Expression of TAT102 is seen in 14 of 15 ovarian epithelial malignancies (adenocarcinoma, epithelial surface tumors, endometrioid Ca). Also, 8 of 9 endometrial adenocarcinomas of the uterus express TAT102. Moreover, expression of TAT102 is seen in 24 of 27 non-small cell lung cancers, positive cases include squamous and adenocarcinomas. Expression in these tumor tissues is significantly higher than in their normal tissue counterparts.

(36) DNA246430 (TAT109)

Fourteen of 92 breast tumor samples are positive for TAT109 expression. Expression in all normal tissues is undetectable.

(37) DNA264454 (TAT106)

Expression of TAT106 is observed in 38/88 breast tumors. Expression in normal breast tissue is weak or undetectable.

(38) DNA98565 (TAT145)

Positive signal for TAT145 was observed in most gliomas, glioblastomas, some melanomas, and normal brain (primarily localized to astrocytes). The signal intensity in the glioblastomas appeared to be greater than that in normal astrocytes. While the majority of glioma and glioblastoma samples tested were positive for TAT145 expression, the majority of normal brain samples tested were negative for such expression.

(39) DNA246435 (TAT152)

Positive signal for TAT152 was observed in most glioblastomas, some melanomas, and normal brain (primarily localized to astrocytes). The signal intensity in the glioblastomas appeared to be greater than that in normal astrocytes. While the majority of glioma and glioblastoma samples tested were positive for TAT152 expression, the majority of normal brain samples tested were negative for such expression.

(40) DNA167234 (TAT130)

Seventy cases of primary adenocarcinoma of the prostate were available for review. Of these 70 cases, 56 cases (80%) are positive for TAT130 expression. TAT130 expression in non-prostatic tissues is weak or undetectable.

(41) DNA235621 (TAT166)

Seventy cases of primary adenocarcinoma of the prostate were available for review. Of these 70 cases, 56 cases (80%) are positive for TAT166 expression. TAT166 expression in non-prostatic tissues is weak or undetectable.

(42) DNA226493 (TAT141)

Positive expression is observed in 70/148 breast carcinomas, 2/63 colorectal adenocarcinomas, 4/42 ovarian tumors, 9/69 non small cell lung carcinomas, 9/67 prostate adenocarcinomas and 5/25 gliomas. Expression in normal non-cancerous tissues appears restricted to prostate and breast epithelium.

(43) DNA226094 (TAT164)

Twenty one of 37 glioblastoma samples and 8 or 8 glioma samples were positive for TAT164 expression while all other tumor and normal tissues examined (including normal brain tissue) were negative.

(44) DNA227578 (TAT165)

Fifteen of 25 glioblastoma samples tested were positive for expression while significantly weaker expression was observed in the normal brain samples tested.

EXAMPLE 5: Immunohistochemistry Analysis

Antibodies against certain TAT polypeptides disclosed herein were prepared and immunohistochemistry analysis was performed as follows. Tissue sections were first fixed for 5 minutes in acetone/ethanol (frozen or paraffin-embedded). The sections were then washed in PBS and then blocked with avidin and biotin (Vector kit) for 10 minutes each followed by a wash in PBS. The sections were then blocked with 10% serum for 20 minutes and then blotted to remove the excess. A primary antibody was then added to the sections at a concentration of 10μg/ml for 1 hour and then the sections were washed in PBS. A biotinylated secondary antibody (anti-primary antibody) was then added to the sections for 30 minutes and then the sections were washed with PBS. The sections were then exposed to the reagents of the Vector ABC kit for 30 minutes and then the sections were washed in PBS. The sections were then exposed to Diaminobenzidine (Pierce) for 5 minutes and then washed in PBS. The sections were then counterstained with Mayers hematoxylin, covered with a coverslip and visualized. Immunohistochemistry analysis can also be performed as described in Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989 and Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). The results from these analyses are show below.

(1) DNA96930 (TAT112)

Significantly higher expression was detected in the apical surface of the colonic crypts of colon tumors than on the apical surface of the normal colonic crypts. Additionally, TAT112 was found to be significantly overexpressed in pancreatic adenocarcinoma cells as compared to normal pancreatic cells. Finally, IHC analysis performed as described above evidenced that TAT112 is significantly overexpressed in lung carcinoma as compared to normal lung tissue, non small cell lung carcinoma as compared to normal lung tissue and stomach carcinoma as compared to normal stomach tissue.

(2) DNA226539 (TAT126)

Positive expression is observed in 2/10 uterine adenocarcinomas, 9/17 ovarian adenocarcinomas and 2/20 non small cell lung carcinomas. Using this procedure, expression of TAT126 was not detectable in any normal tissue.

(3) DNA236511 (TAT151)

Positive expression is observed in 2/10 uterine adenocarcinomas, 9/17 ovarian adenocarcinomas and 2/20 non small cell lung carcinomas. Using this procedure, expression of TAT151 was not detectable in any normal tissue.

EXAMPLE 6: Verification and Analysis of Differential TAT Polypeptide Expression by GEPIS

TAT polypeptides which may have been identified as a tumor antigen as described in one or more of the above Examples were analyzed and verified as follows. An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and interesting EST sequences were identified by GEPIS. Gene expression profiling *in silico* (GEPIS) is a bioinformatics tool developed at Genentech, Inc. that characterizes genes of interest for new cancer therapeutic targets. GEPIS takes advantage of large amounts of EST sequence and library information to determine gene expression profiles. GEPIS is

capable of determining the expression profile of a gene based upon its proportional correlation with the number of its occurrences in EST databases, and it works by integrating the LIFESEQ® EST relational database and Genentech proprietary information in a stringent and statistically meaningful way. In this example, GEPIS is used to identify and cross-validate novel tumor antigens, although GEPIS can be configured to perform either very specific analyses or broad screening tasks. For the initial screen, GEPIS is used to identify EST sequences from the LIFESEQ® database that correlate to expression in a particular tissue or tissues of interest (often a tumor tissue of interest). The EST sequences identified in this initial screen (or consensus sequences obtained from aligning multiple related and overlapping EST sequences obtained from the initial screen) were then subjected to a screen intended to identify the presence of at least one transmembrane domain in the encoded protein. Finally, GEPIS was employed to generate a complete tissue expression profile for the various sequences of interest. Using this type of screening bioinformatics, various TAT polypeptides (and their encoding nucleic acid molecules) were identified as being significantly overexpressed in a particular type of cancer or certain cancers as compared to other cancers and/or normal non-cancerous tissues. The rating of GEPIS hits is based upon several criteria including, for example, tissue specificity, tumor specificity and expression level in normal essential and/or normal proliferating tissues. The following is a list of molecules whose tissue expression profile as determined by GEPIS evidences high tissue expression and significant upregulation of expression in a specific tumor or tumors as compared to other tumor(s) and/or normal tissues and optionally relatively low expression in normal essential and/or normal proliferating tissues. As such, the molecules listed below are excellent polypeptide targets for the diagnosis and therapy of cancer in mammals.

Molecule	upregulation of expression in:	as compared to:
DNA77507 (TAT161)	breast tumor	normal breast tissue
DNA77507 (TAT161)	colon tumor	normal colon tissue
DNA77507 (TAT161)	lung tumor	normal lung tissue
DNA77507 (TAT161)	kidney tumor	normal kidney tissue
DNA77507 (TAT161)	liver tumor	normal liver tissue
DNA77507 (TAT161)	ovarian tumor	normal ovarian tissue
DNA77507 (TAT161)	pancreatic tumor	normal pancreatic tissue
DNA77507 (TAT161)	rectum tumor	normal rectum tissue
DNA77507 (TAT161)	skin tumor	normal skin tissue
DNA77507 (TAT161)	uterine tumor	normal uterine tissue
DNA77507 (TAT161)	brain tumor	normal brain tissue
DNA77507 (TAT161)	soft tissue tumor	normal soft tissue
DNA77507 (TAT161)	bone tumor	normal bone tissue
DNA82343 (TAT157)	colon tumor	normal colon tissue
DNA82343 (TAT157)	ovarian tumor	normal ovarian tissue
DNA82343 (TAT157)	stomach tumor	normal stomach tissue
DNA82343 (TAT157)	thymus tumor	normal thymus tissue
DNA82343 (TAT157)	small intestine tumor	normal small intestine tissue
DNA87994 (TAT160)	breast tumor	normal breast tissue
DNA87994 (TAT160)	pancreatic tumor	normal pancreatic tissue
DNA87994 (TAT160)	colon tumor	normal colon tissue
DNA87994 (TAT160)	esophagus tumor	normal esophagus tissue
DNA87994 (TAT160)	ovarian tumor	normal ovarian tissue
DNA87994 (TAT160)	prostate tumor	normal prostate tissue
DNA88131 (TAT158)	breast tumor	normal breast tissue
DNA88131 (TAT158)	colon tumor	normal colon tissue
DNA88131 (TAT158)	lung tumor	normal lung tissue

Molecule	upregulation of expressioo in:	as compared to:
DNA88131 (TAT158)	pancreatic tumor	normal pancreatic tissue
DNA88131 (TAT158)	prostate tumor	normal prostate tissue
DNA88131 (TAT158)	stomach tumor	normal stomach tissue
DNA88131 (TAT158)	bladder tumor	normal bladder tissue
DNA88131 (TAT158)	brain tumor	normal brain tissue
DNA95930 (TAT110)	colon tumor	normal colon tissue
DNA95930 (TAT110)	lung tumor	normal lung tissue
DNA95930 (TAT110)	prostate tumor	normal prostate tissue
DNA95930 (TAT110)	endometrial tumor	normal endometrial tissue
DNA95930 (TAT110)	ovarian tumor	normal ovarian tissue
DNA95930 (TAT110)	breast tumor	normal breast tissue
DNA95930-1 (TAT210)	colon tumor	normal colon tissue
DNA95930-1 (TAT210)	lung tumor	normal lung tissue
DNA95930-1 (TAT210)	prostate tumor	normal prostate tissue
DNA95930-1 (TAT210)	endometrial tumor	normal endometrial tissue
DNA95930-1 (TAT210)	ovarian tumor	normal ovarian tissue
DNA95930-1 (TAT210)	breast tumor	normal breast tissue
DNA96917 (TAT159)	pancreatic tumor	normal pancreatic tissue
DNA96917 (TAT159)	lung tumor	normal lung tissue
DNA96917 (TAT159)	liver tumor	normal liver tissue
DNA96917 (TAT159)	prostate tumor	normal prostate tissue
DNA96930 (TAT112)	breast tumor	normal breast tissue
DNA96930 (TAT112)	colon tumor	normal colon tissue
DNA96930 (TAT112)	lung tumor	normal lung tissue
DNA96930 (TAT112)	ovarian tumor	normal ovarian tissue
DNA96930 (TAT112)	pancreatic tumor	normal pancreatic tissue
DNA96930 (TAT112)	stomach tumor	normal stomach tissue
DNA96936 (TAT147)	breast tumor	normal breast tissue
DNA96936 (TAT147)	colon tumor	normal colon tissue
DNA96936 (TAT147)	prostate tumor	normal prostate tissue
DNA96936 (TAT147)	uterine tumor	normal uterine tissue
DNA98565 (TAT145)	brain tumor	normal brain tissue
DNA98565 (TAT145)	colon tumor	normal colon tissue
DNA246435 (TAT152)	brain tumor	normal brain tissue
DNA246435 (TAT152)	colon tumor	normal colon tissue
DNA98591 (TAT162)	colon tumor	normal colon tissue
DNA98591 (TAT162)	small intestine tumor	normal small intestine tissue
DNA98591 (TAT162)	ovarian tumor	normal ovarian tissue
DNA98591 (TAT162)	esophagus tumor	normal esophagus tissue
DNA108809 (TAT114)	colon tumor	normal colon tissue
DNA108809 (TAT114)	lung tumor	normal lung tissue
DNA108809 (TAT114)	ovarian tumor	normal ovarian tissue
DNA108809 (TAT114)	brain tumor	normal brain tissue
DNA143493 (TAT103)	breast tumor	normal breast tissue
DNA167234 (TAT130)	prostate tumor	normal prostate tissue
DNA235621 (TAT166)	prostate tumor	normal prostate tissue
DNA176766 (TAT132)	kidney tumor	normal kidney tissue
DNA176766 (TAT132)	uterine tumor	normal uterine tissue
DNA236463 (TAT150)	kidney tumor	normal kidney tissue
DNA236463 (TAT150)	uterine tumor	normal uterine tissue
DNA181162 (TAT129)	prostate tumor	normal prostate tissue
DNA188221 (TAT111)	colon tumor	normal colon tissue
DNA188221 (TAT111)	liver tumor	normal liver tissue
DNA188221 (TAT111)	lung tumor	normal lung tissue
DNA233876 (TAT146)	colon tumor	normal colon tissue

Molecule	upregulation of expression in:	as compared to:
DNA233876 (TAT146)	liver tumor	normal liver tissue
DNA233876 (TAT146)	lung tumor	normal lung tissue
DNA193891 (TAT148)	prostate tumor	normal prostate tissue
DNA193891 (TAT148)	breast tumor	normal breast tissue
DNA248170 (TAT187)	breast tumor	normal breast tissue
DNA248170 (TAT187)	prostate tumor	normal prostate tissue
DNA194628 (TAT118)	kidney tumor	normal kidney tissue
DNA246415 (TAT167)	kidney tumor	normal kidney tissue
DNA215609 (TAT113)	colon tumor	normal colon tissue
DNA220432 (TAT128)	prostate tumor	normal prostate tissue
DNA226094 (TAT164)	breast tumor	normal breast tissue
DNA226094 (TAT164)	brain tumor	normal brain tissue
DNA226094 (TAT164)	ovarian tumor	normal ovarian tissue
DNA226094 (TAT164)	lung tumor	normal lung tissue
DNA226165 (TAT122)	breast tumor	normal breast tissue
DNA226165 (TAT122)	endometrial tumor	normal endometrial tissue
DNA226165 (TAT122)	lung tumor	normal lung tissue
DNA226165 (TAT122)	colon tumor	normal colon tissue
DNA226237 (TAT117)	kidney tumor	normal kidney tissue
DNA246450 (TAT168)	kidney tumor	normal kidney tissue
DNA246450 (TAT168)	brain tumor	normal brain tissue
DNA226456 (TAT144)	breast tumor	normal breast tissue
DNA226456 (TAT144)	brain tumor	normal brain tissue
DNA226456 (TAT144)	endometrial tumor	normal endometrial tissue
DNA226456 (TAT144)	kidney tumor	normal kidney tissue
DNA226456 (TAT144)	lung tumor	normal lung tissue
DNA237637 (TAT188)	breast tumor	normal breast tissue
DNA237637 (TAT188)	brain tumor	normal brain tissue
DNA237637 (TAT188)	endometrial tumor	normal endometrial tissue
DNA237637 (TAT188)	kidney tumor	normal kidney tissue
DNA237637 (TAT188)	lung tumor	normal lung tissue
DNA226539 (TAT126)	colon tumor	normal colon tissue
DNA226539 (TAT126)	endometrial tumor	normal endometrial tissue
DNA226539 (TAT126)	ovarian tumor	normal ovarian tissue
DNA226539 (TAT126)	pancreatic tumor	normal pancreatic tissue
DNA236511 (TAT151)	colon tumor	normal colon tissue
DNA236511 (TAT151)	endometrial tumor	normal endometrial tissue
DNA236511 (TAT151)	ovarian tumor	normal ovarian tissue
DNA236511 (TAT151)	pancreatic tumor	normal pancreatic tissue
DNA226771 (TAT115)	colon tumor	normal colon tissue
DNA227087 (TAT163)	breast tumor	normal breast tissue
DNA227087 (TAT163)	colon tumor	normal colon tissue
DNA227087 (TAT163)	endocrine tumor	normal endocrine tissue
DNA227087 (TAT163)	kidney tumor	normal kidney tissue
DNA227087 (TAT163)	liver tumor	normal liver tissue
DNA227087 (TAT163)	lung tumor	normal lung tissue
DNA227087 (TAT163)	pancreatic tumor	normal pancreatic tissue
DNA227087 (TAT163)	uterine tumor	normal uterine tissue
DNA227087 (TAT163)	prostate tumor	normal prostate tissue
DNA227087 (TAT163)	bladder tumor	normal bladder tissue
DNA266307 (TAT227)	breast tumor	normal breast tissue
DNA266307 (TAT227)	colon tumor	normal colon tissue
DNA266307 (TAT227)	endocrine tumor	normal endocrine tissue
DNA266307 (TAT227)	kidney tumor	normal kidney tissue
DNA266307 (TAT227)	liver tumor	normal liver tissue

Molecule	upregulation of expression in:	as compared to:
DNA266307 (TAT227)	lung tumor	normal lung tissue
DNA266307 (TAT227)	pancreatic tumor	normal pancreatic tissue
DNA266307 (TAT227)	uterine tumor	normal uterine tissue
DNA266307 (TAT227)	prostate tumor	normal prostate tissue
DNA266307 (TAT227)	bladder tumor	normal bladder tissue
DNA266311 (TAT228)	breast tumor	normal breast tissue
DNA266311 (TAT228)	colon tumor	normal colon tissue
DNA266311 (TAT228)	endocrine tumor	normal endocrine tissue
DNA266311 (TAT228)	kidney tumor	normal kidney tissue
DNA266311 (TAT228)	liver tumor	normal liver tissue
DNA266311 (TAT228)	lung tumor	normal lung tissue
DNA266311 (TAT228)	pancreatic tumor	normal pancreatic tissue
DNA266311 (TAT228)	uterine tumor	normal uterine tissue
DNA266311 (TAT228)	prostate tumor	normal prostate tissue
DNA266311 (TAT228)	bladder tumor	normal bladder tissue
DNA266312 (TAT229)	breast tumor	normal breast tissue
DNA266312 (TAT229)	colon tumor	normal colon tissue
DNA266312 (TAT229)	endocrine tumor	normal endocrine tissue
DNA266312 (TAT229)	kidney tumor	normal kidney tissue
DNA266312 (TAT229)	liver tumor	normal liver tissue
DNA266312 (TAT229)	lung tumor	normal lung tissue
DNA266312 (TAT229)	pancreatic tumor	normal pancreatic tissue
DNA266312 (TAT229)	uterine tumor	normal uterine tissue
DNA266312 (TAT229)	prostate tumor	normal prostate tissue
DNA266312 (TAT229)	bladder tumor	normal bladder tissue
DNA266313 (TAT230)	breast tumor	normal breast tissue
DNA266313 (TAT230)	colon tumor	normal colon tissue
DNA266313 (TAT230)	endocrine tumor	normal endocrine tissue
DNA266313 (TAT230)	kidney tumor	normal kidney tissue
DNA266313 (TAT230)	liver tumor	normal liver tissue
DNA266313 (TAT230)	lung tumor	normal lung tissue
DNA266313 (TAT230)	pancreatic tumor	normal pancreatic tissue
DNA266313 (TAT230)	uterine tumor	normal uterine tissue
DNA266313 (TAT230)	prostate tumor	normal prostate tissue
DNA266313 (TAT230)	bladder tumor	normal bladder tissue
DNA227224 (TAT121)	breast tumor	normal breast tissue
DNA227224 (TAT121)	endometrial tumor	normal endometrial tissue
DNA227224 (TAT121)	lung tumor	normal lung tissue
DNA227224 (TAT121)	skin tumor	normal skin tissue
DNA247486 (TAT183)	breast tumor	normal breast tissue
DNA247486 (TAT183)	endometrial tumor	normal endometrial tissue
DNA247486 (TAT183)	lung tumor	normal lung tissue
DNA247486 (TAT183)	skin tumor	normal skin tissue
DNA227578 (TAT165)	brain tumor	normal brain tissue
DNA227800 (TAT131)	prostate tumor	normal prostate tissue
DNA227800 (TAT131)	kidney tumor	normal kidney tissue
DNA227904 (TAT140)	breast tumor	normal breast tissue
DNA228199 (TAT127)	uterine tumor	normal uterine tissue
DNA228199 (TAT127)	fallopian tube tumor	normal fallopian tube tissue
DNA228199 (TAT127)	ovarian tumor	normal ovarian tissue
DNA228199 (TAT127)	lung tumor	normal lung tissue
DNA228201 (TAT116)	colon tumor	normal colon tissue
DNA247488 (TAT189)	colon tumor	normal colon tissue
DNA236538 (TAT190)	colon tumor	normal colon tissue
DNA247489 (TAT191)	colon tumor	normal colon tissue

Molecule	upregulation of expression in:	as compared to:
DNA231312 (TAT143)	colon tumor	normal colon tissue
DNA231542 (TAT100)	brain tumor	normal brain tissue
DNA231542 (TAT100)	glioma	normal glial tissue
DNA231542-1 (TAT284)	brain tumor	normal brain tissue
DNA231542-1 (TAT284)	glioma	normal glial tissue
DNA231542-2 (TAT285)	brain tumor	normal brain tissue
DNA231542-2 (TAT285)	glioma	normal glial tissue
DNA297393 (TAT285-1)	brain tumor	normal brain tissue
DNA297393 (TAT285-1)	glioma	normal glial tissue
DNA232754 (TAT125)	lung tumor	normal lung tissue
DNA236246 (TAT153)	breast tumor	normal breast tissue
DNA236343 (TAT104)	breast tumor	normal breast tissue
DNA236493 (TAT141)	breast tumor	normal breast tissue
DNA236493 (TAT141)	glioblastoma tumor	normal glial tissue
DNA236534 (TAT102)	breast tumor	normal breast tissue
DNA236534 (TAT102)	lung tumor	normal lung tissue
DNA236534 (TAT102)	pancreatic tumor	normal pancreatic tissue
DNA236534 (TAT102)	prostate tumor	normal prostate tissue
DNA236534 (TAT102)	bladder tumor	normal bladder tissue
DNA247480 (TAT142)	lung tumor	normal lung tissue
DNA264454 (TAT106)	breast tumor	normal breast tissue
DNA264454 (TAT106)	prostate tumor	normal prostate tissue
DNA264454 (TAT106)	ovarian tumor	normal ovarian tissue

EXAMPLE 7: Use of TAT as a hybridization probe

The following method describes use of a nucleotide sequence encoding TAT as a hybridization probe for, i.e., diagnosis of the presence of a tumor in a mammal.

DNA comprising the coding sequence of full-length or mature TAT as disclosed herein can also be employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of TAT) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled TAT-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence TAT can then be identified using standard techniques known in the art.

EXAMPLE 8: Expression of TAT in *E. coli*

This example illustrates preparation of an unglycosylated form of TAT by recombinant expression in *E. coli*.

The DNA sequence encoding TAT is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and

tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the TAT coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized TAT protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

TAT may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding TAT is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g $(NH_4)_2SO_4$, 0.71 g sodium citrate•2H2O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM $MgSO_4$) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the

desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded TAT polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 9: Expression of TAT in mammalian cells

This example illustrates preparation of a potentially glycosylated form of TAT by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the TAT DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the TAT DNA using ligation methods such as described in Sambrook et al., supra. The resulting vector is called pRK5-TAT.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 μg pRK5-TAT DNA is mixed with about 1 μg DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500 μl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M $CaCl_2$. To this mixture is added, dropwise, 500 μl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM $NaPO_4$, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The

293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 μCi/ml ^{35}S-cysteine and 200 μCi/ml ^{35}S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of TAT polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, TAT may be introduced into 293 cells transiently using the dextran sulfate method described by Somparyrac et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 μg pRK5-TAT DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 μg/ml bovine insulin and 0.1 μg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed TAT can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, TAT can be expressed in CHO cells. The pRK5-TAT can be transfected into CHO cells using known reagents such as $CaPO_4$ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ^{35}S-methionine. After determining the presence of TAT polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed TAT can then be concentrated and purified by any selected method.

Epitope-tagged TAT may also be expressed in host CHO cells. The TAT may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged TAT insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged TAT can then be concentrated and purified by any selected method, such as by Ni^{2+}-chelate affinity chromatography.

TAT may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesit), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Qiagen), Dosper® or Fugene® (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3 x 10^7 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μm filtered PS20 with 5% 0.2 μm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3 x 10^5 cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2 x 10^6 cells/mL. On day 0, the cell number pH ie determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μm filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting

1 ml fractions into tubes containing 275 μL of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 10: Expression of TAT in Yeast

The following method describes recombinant expression of TAT in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of TAT from the ADH2/GAPDH promoter. DNA encoding TAT and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of TAT. For secretion, DNA encoding TAT can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native TAT signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of TAT.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant TAT can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing TAT may further be purified using selected column chromatography resins.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 11: Expression of TAT in Baculovirus-Infected Insect Cells

The following method describes recombinant expression of TAT in Baculovirus-infected insect cells.

The sequence coding for TAT is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding TAT or the desired portion of the coding sequence of TAT such as the sequence encoding an extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley

et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged TAT can then be purified, for example, by Ni^{2+}-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM $MgCl_2$; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 μm filter. A Ni^{2+}-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A_{280} with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A_{280} baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni^{2+}-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His_6-tagged TAT are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) TAT can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 12: Preparation of Antibodies that Bind TAT

This example illustrates preparation of monoclonal antibodies which can specifically bind TAT.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, supra. Immunogens that may be employed include purified TAT, fusion proteins containing TAT, and cells expressing recombinant TAT on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the TAT immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-TAT antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of TAT. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells

which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against TAT. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against TAT is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-TAT monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

Antibodies directed against certain of the TAT polypeptides disclosed herein have been successfully produced using this technique(s). More specifically, functional monoclonal antibodies that are capable of recognizing and binding to TAT protein (as measured by standard ELISA, FACS sorting analysis and/or immunohistochemistry analysis) have been successfully generated against the following TAT proteins as disclosed herein: TAT110 (DNA95930), TAT210 (DNA95930-1), TAT113 (DNA215609), TAT126 (DNA226539), TAT151 (DNA236511), TAT111 (DNA188221), TAT146 (DNA233876), TAT112 (DNA96930), TAT145 (DNA98565), TAT152 (DNA246435), TAT141 (DNA236493), TAT114 (DNA108809), TAT104 (DNA236343), TAT100 (DNA231542), TAT284 (DNA231542-1), TAT285 (DNA231542-2), TAT285-1 (DNA297393), TAT144 (DNA226456), TAT188 (DNA237637), TAT123 (DNA210499), TAT211 (DNA219894), TAT102 (DNA236334), TAT127 (DNA228199) and TAT128 (DNA220432). Interestingly, Applicants have identified that the monoclonal antibodies prepared against TAT111 (DNA188221) and TAT146 (DNA233876) are capable of blocking activation of the EphB2R receptor encoded by the DNA188221 and DNA233876 molecules by its associated ligand polypeptide. As such, antibodies and methods for using those antibodies for blocking activation of the EphB2R receptor (i.e., TAT111 and TAT146 polypeptides) by its associated ligand are encompassed within the presently described invention. Moreover, Applicants have identified that monoclonal antibodies directed against the TAT110 (DNA95930) and TAT210 (DNA95930-1) polypeptides (i.e., IL-20 receptor alpha polypeptides) are capable of inhibiting activation of the IL20 receptor alpha by IL-19 protein.As such, antibodies and methods for using those antibodies for inhibiting activation of the IL-20 receptor alpha (i.e., TAT110 and TAT210 polypeptides) by IL-19 are encompassed within the presently described invention.

In addition to the successful preparation of monoclonal antibodies directed against the TAT polypeptides as described herein, many of those monoclonal antibodies have been successfully conjugated to a cell toxin for use in directing the cellular toxin to a cell (or tissue) that expresses a TAT polypeptide of interested (both *in vitro* and *in vivo*). For example, toxin (e.g., DM1) derivitized monoclonal antibodies have been successfully generated to the following TAT polypeptides as described herein: TAT110 (DNA95930), TAT210 (DNA95930-1), TAT112 (DNA96930), TAT113 (DNA215609), TAT111 (DNA188221) and TAT146 (DNA233876).

EXAMPLE 13: Purification of TAT Polypeptides Using Specific Antibodies

Native or recombinant TAT polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-TAT polypeptide, mature TAT polypeptide, or pre-TAT polypeptide is purified by immunoaffinity chromatography using antibodies specific for the TAT polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-TAT polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of TAT polypeptide by preparing a fraction from cells containing TAT polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble TAT polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble TAT polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of TAT polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/TAT polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and TAT polypeptide is collected.

EXAMPLE 14: *In Vitro* Tumor Cell Killing Assay

Mammalian cells expressing the TAT polypeptide of interest may be obtained using standard expression vector and cloning techniques. Alternatively, many tumor cell lines expressing TAT polypeptides of interest are publicly available, for example, through the ATCC and can be routinely identified using standard ELISA or FACS analysis. Anti-TAT polypeptide monoclonal antibodies (and toxin conjugated derivatives thereof) may then be employed in assays to determine the ability of the antibody to kill TAT polypeptide expressing cells *in vitro*.

For example, cells expressing the TAT polypeptide of interest are obtained as described above and plated into 96 well dishes. In one analysis, the antibody/toxin conjugate (or naked antibody) is included throughout the cell incubation for a period of 4 days. In a second independent analysis, the cells are incubated for 1 hour with the antibody/toxin conjugate (or naked antibody) and then washed and incubated in the absence of antibody/toxin conjugate for a period of 4 days. Cell viability is then measured using the CellTiter-Glo Luminescent Cell Viability Assay from Promega (Cat# G7571). Untreated cells serve as a negative control.

In one specific analysis, the ability of monoclonal antibodies directed against TAT112 (DNA96930) were analyzed for the ability to kill cells expressing that polypeptide. In one analysis, an expression vector called gD.NCA was prepared. The TAT112 polypeptide encoding sequences inserted into that vector are driven by an SV40 promoter and the vector also contains the SV40 early poly A signal. The gD.NCA vector was co-transfected into PC3 cells along with an SV40 vector that expresses Neo resistance in PC3 cells, and positive transformants were selected in 800 μg/ml G418. Positive clones were isolated in 96 well plates and analyzed by flow cytometry using an anti-TAT112 monoclonal antibody prepared as described above and called 3E6. Clone 3 was selected for the analysis as it was found to express a high level of TAT112 polypeptide on its surface. In a second independent analysis, the pancreatic cancer cell line, Hpaf II, was obtained from the ATCC and employed in the assay.

The results from the above described assay demonstrated that DM1-conjugated anti-TAT112 monoclonal antibodies were highly efficacious in killing both the TAT112 expressing PC3 cell line as well as the pancreatic cancer cell line Hpaf II as compared to the untreated negative controls.

EXAMPLE 15: *In Vivo* Tumor Cell Killing Assay

To test the efficacy of unconjugated anti-TAT112 monoclonal antibodies, anti-TAT112 antibody was injected intraperitoneally into nude mice 24 hours prior to receiving PC3.gD.NCA clone 3 cells (obtained as described in Example 14 above) subcutaneously in the flank. Antibody injections continued twice per week for the remainder of the study. Tumor volume was measured twice per week.

To test the efficacy of DM1-conjugated anti-TAT112 antibody, PC3.gD.NCA clone 3 cells (obtained as described in Example 14 above) were inoculated into the flank of nude mice. When the tumors reached a mean volume of approximately 100mm3, mice were treated with DM1-conjugated anti-TAT112 antibody intravenously either once or twice per week.

The results of the above analyses demonstrated that both the unconjugated anti-TAT112 as well as the DM1-conjugated anti-TAT112 antibody were highly efficacious in reducing tumor volume in this *in vivo* model. These analyses demonstrate that anti-TAT polypeptide monoclonal antibodies are efficacious for killing tumor cells that express a TAT polypeptide of interest.

EXAMPLE 16: Northern Blot Analysis

Northern blot analysis was performed essentially as described by Sambrook et al., supra. Northern blot analysis using probes derived from DNA231542, DNA231542-1, DNA231542-2 and DNA297393 evidences significant upregulation of expression in human glioma tissue as compared to normal human brain tissue.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any

aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to a polypeptide having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

2. An isolated antibody that binds to a polypeptide having:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

3. The antibody of Claim 1 which is a monoclonal antibody.

4. The antibody of Claim 1 which is an antibody fragment.

5. The antibody of Claim 1 which is a chimeric or a humanized antibody.

6. The antibody of Claim 1 which is conjugated to a growth inhibitory agent.

7. The antibody of Claim 1 which is conjugated to a cytotoxic agent.

8. The antibody of Claim 7, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

9. The antibody of Claim 7, wherein the cytotoxic agent is a toxin.

10. The antibody of Claim 9, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

11. The antibody of Claim 9, wherein the toxin is a maytansinoid.

12. The antibody of Claim 1 which is produced in bacteria.

13. The antibody of Claim 1 which is produced in CHO cells.

14. The antibody of Claim 1 which induces death of a cell to which it binds.

15. The antibody of Claim 1 which is detectably labeled.

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(54) Title: COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF TUMOR

(57) Abstract: The present invention is directed to compositions of matter useful for the diagnosis and treatment of tumor in mammals and to methods of using those compositions of matter for the same.

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, GenCore databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,965,710 A (BODMER et al) 12 October 1999 (12.10.1999), column 9, lines 14-19; column 10, lines 10-11; Example 6 of columns 17-19; Sequence 34 within columns 49-52 and attached database sheet.	1-9 and 12-15
Y	US 4,331,598 A (HASEGAWA et al) 25 May 1982 (25.05.1982), abstract, column 16, lines 65-68.	10 and 11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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(54) Title: COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF TUMOR

(57) Abstract: The present invention is directed to compositions of matter useful for the diagnosis and treatment of tumor in mammals and to methods of using these compositions of matter for the same.

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COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF TUMOR

FIELD OF THE INVENTION

The present invention is directed to compositions of matter useful for the diagnosis and treatment of tumor in mammals and to methods of using these compositions of matter for the same.

BACKGROUND OF THE INVENTION

Malignant tumors (cancers) are the second leading cause of death in the United States, after heart disease (Boring et al., *CA Cancer J. Clin.* 43:7 (1993)). Cancer is characterized by the increase in the number of abnormal, or neoplastic, cells derived from a normal tissue which proliferate to form a tumor mass, the invasion of adjacent tissues by these neoplastic tumor cells, and the generation of malignant cells which eventually spread via the blood or lymphatic system to regional lymph nodes and to distant sites via a process called metastasis. In a cancerous state, a cell proliferates under conditions in which normal cells would not grow. Cancer manifests itself in a wide variety of forms, characterized by different degrees of invasiveness and aggressiveness.

In attempts to discover effective cellular targets for cancer diagnosis and therapy, researchers have sought to identify transmembrane or otherwise membrane-associated polypeptides that are specifically expressed on the surface of one or more particular type(s) of cancer cell as compared to on one or more normal non-cancerous cell(s). Often, such membrane-associated polypeptides are more abundantly expressed on the surface of the cancer cells as compared to on the surface of the non-cancerous cells. The identification of such tumor-associated cell surface antigen polypeptides has given rise to the ability to specifically target cancer cells for destruction via antibody-based therapies. In this regard, it is noted that antibody-based therapy has proved very effective in the treatment of certain cancers. For example, HERCEPTIN® and RITUXAN® (both from Genentech Inc., South San Francisco, California) are antibodies that have been used successfully to treat breast cancer and non-Hodgkin's lymphoma, respectively. More specifically, HERCEPTIN® is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2) proto-oncogene. HER2 protein overexpression is observed in 25-30% of primary breast cancers. RITUXAN® is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Both these antibodies are recombinantly produced in CHO cells.

In other attempts to discover effective cellular targets for cancer diagnosis and therapy, researchers have sought to identify (1) non-membrane-associated polypeptides that are specifically produced by one or more particular type(s) of cancer cell(s) as compared to by one or more particular type(s) of non-cancerous normal cell(s), (2) polypeptides that are produced by cancer cells at an expression level that is significantly higher than that of one or more normal non-cancerous cell(s), or (3) polypeptides whose expression is

specifically limited to only a single (or very limited number of different) tissue type(s) in both the cancerous and non-cancerous state (e.g., normal prostate and prostate tumor tissue). Such polypeptides may remain intracellularly located or may be secreted by the cancer cell. Moreover, such polypeptides may be expressed not by the cancer cell itself, but rather by cells which produce and/or secrete polypeptides having a potentiating or growth-enhancing effect on cancer cells. Such secreted polypeptides are often proteins that provide cancer cells with a growth advantage over normal cells and include such things as, for example, angiogenic factors, cellular adhesion factors, growth factors, and the like. Identification of antagonists of such non-membrane associated polypeptides would be expected to serve as effective therapeutic agents for the treatment of such cancers. Furthermore, identification of the expression pattern of such polypeptides would be useful for the diagnosis of particular cancers in mammals.

Despite the above identified advances in mammalian cancer therapy, there is a great need for additional diagnostic and therapeutic agents capable of detecting the presence of tumor in a mammal and for effectively inhibiting neoplastic cell growth, respectively. Accordingly, it is an objective of the present invention to identify: (1) cell membrane-associated polypeptides that are more abundantly expressed on one or more type(s) of cancer cell(s) as compared to on normal cells or on other different cancer cells, (2) non-membrane-associated polypeptides that are specifically produced by one or more particular type(s) of cancer cell(s) (or by other cells that produce polypeptides having a potentiating effect on the growth of cancer cells) as compared to by one or more particular type(s) of non-cancerous normal cell(s), (3) non-membrane-associated polypeptides that are produced by cancer cells at an expression level that is significantly higher than that of one or more normal non-cancerous cell(s), or (4) polypeptides whose expression is specifically limited to only a single (or very limited number of different) tissue type(s) in both a cancerous and non-cancerous state (e.g., normal prostate and prostate tumor tissue), and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of cancer in mammals. It is also an objective of the present invention to identify cell membrane-associated, secreted or intracellular polypeptides whose expression is limited to a single or very limited number of tissues, and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of cancer in mammals.

SUMMARY OF THE INVENTION

A. Embodiments

In the present specification, Applicants describe for the first time the identification of various cellular polypeptides (and their encoding nucleic acids or fragments thereof) which are expressed to a greater degree on the surface of or by one or more types of cancer cell(s) as compared to on the surface of or by one or more types of normal non-cancer cells. Alternatively, such polypeptides are expressed by cells which produce and/or secrete polypeptides having a potentiating or growth-enhancing effect on cancer cells. Again alternatively, such polypeptides may not be overexpressed by tumor cells as compared to normal cells of the same tissue type, but rather may be specifically expressed by both tumor cells and normal cells of only a single or very limited number of tissue types (preferably tissues which are not essential for life, e.g., prostate, etc.).

All of the above polypeptides are herein referred to as Tumor-associated Antigenic Target polypeptides ("TAT" polypeptides) and are expected to serve as effective targets for cancer therapy and diagnosis in mammals.

Accordingly, in one embodiment of the present invention, the invention provides an isolated nucleic acid molecule having a nucleotide sequence that encodes a tumor-associated antigenic target polypeptide or fragment thereof (a "TAT" polypeptide).

In certain aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule encoding a full-length TAT polypeptide having an amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule comprising the coding sequence of a full-length TAT polypeptide cDNA as disclosed herein, the coding sequence of a TAT polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In further aspects, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule that encodes the same mature polypeptide encoded by the full-length coding region of any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect of the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a TAT polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide(s) are disclosed herein. Therefore, soluble extracellular domains of the herein described TAT polypeptides are contemplated.

In other aspects, the present invention is directed to isolated nucleic acid molecules which hybridize to (a) a nucleotide sequence encoding a TAT polypeptide having a full-length amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein,

or (b) the complement of the nucleotide sequence of (a). In this regard, an embodiment of the present invention is directed to fragments of a full-length TAT polypeptide coding sequence, or the complement thereof, as disclosed herein, that may find use as, for example, hybridization probes useful as, for example, diagnostic probes, antisense oligonucleotide probes, or for encoding fragments of a full-length TAT polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-TAT polypeptide antibody, a TAT binding oligopeptide or other small organic molecule that binds to a TAT polypeptide. Such nucleic acid fragments are usually at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a TAT polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the TAT polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which TAT polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such novel fragments of TAT polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the TAT polypeptide fragments encoded by these nucleotide molecule fragments, preferably those TAT polypeptide fragments that comprise a binding site for an anti-TAT antibody, a TAT binding oligopeptide or other small organic molecule that binds to a TAT polypeptide.

In another embodiment, the invention provides isolated TAT polypeptides encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated TAT polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity, to a TAT polypeptide having a full-length amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide protein, with or without the signal peptide, as disclosed herein, an amino acid sequence encoded by any of the nucleic acid sequences disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated TAT polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a specific aspect, the invention provides an isolated TAT polypeptide without the N-terminal signal sequence and/or without the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the TAT polypeptide and recovering the TAT polypeptide from the cell culture.

Another aspect of the invention provides an isolated TAT polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the TAT polypeptide and recovering the TAT polypeptide from the cell culture.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides isolated chimeric polypeptides comprising any of the herein described TAT polypeptides fused to a heterologous (non-TAT) polypeptide. Example of such chimeric molecules comprise any of the herein described TAT polypeptides fused to a heterologous polypeptide such as, for example, an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which binds, preferably specifically, to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, single-chain antibody or antibody that competitively inhibits the binding of an anti-TAT polypeptide antibody to its respective antigenic epitope. Antibodies of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which they bind. For diagnostic purposes, the antibodies of the present invention may be detectably labeled, attached to a solid support, or the like.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described antibodies. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described antibodies is further provided and comprises culturing host cells under conditions suitable for expression of the desired antibody and recovering the desired antibody from the cell culture.

In another embodiment, the invention provides oligopeptides ("TAT binding oligopeptides") which bind, preferably specifically, to any of the above or below described TAT polypeptides. Optionally, the TAT binding oligopeptides of the present invention may be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive

isotope, a nucleolytic enzyme, or the like. The TAT binding oligopeptides of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which they bind. For diagnostic purposes, the TAT binding oligopeptides of the present invention may be detectably labeled, attached to a solid support, or the like.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described TAT binding oligopeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described TAT binding oligopeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired oligopeptide and recovering the desired oligopeptide from the cell culture.

In another embodiment, the invention provides small organic molecules ("TAT binding organic molecules") which bind, preferably specifically, to any of the above or below described TAT polypeptides. Optionally, the TAT binding organic molecules of the present invention may be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The TAT binding organic molecules of the present invention preferably induce death of a cell to which they bind. For diagnostic purposes, the TAT binding organic molecules of the present invention may be detectably labeled, attached to a solid support, or the like.

In a still further embodiment, the invention concerns a composition of matter comprising a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

In yet another embodiment, the invention concerns an article of manufacture comprising a container and a composition of matter contained within the container, wherein the composition of matter may comprise a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein. The article may further optionally comprise a label affixed to the container, or a package insert included with the container, that refers to the use of the composition of matter for the therapeutic treatment or diagnostic detection of a tumor.

Another embodiment of the present invention is directed to the use of a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT polypeptide antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein, for the preparation of a medicament useful in the treatment of a condition which is responsive to the TAT polypeptide, chimeric TAT polypeptide, anti-TAT polypeptide antibody, TAT binding oligopeptide, or TAT binding organic molecule.

B. Additional Embodiments

Another embodiment of the present invention is directed to a method for inhibiting the growth of a cell that expresses a TAT polypeptide, wherein the method comprises contacting the cell with an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, and wherein the binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide causes inhibition of the growth of the cell expressing the TAT polypeptide. In preferred embodiments, the cell is a cancer cell and binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide causes death of the cell expressing the TAT polypeptide. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and TAT binding oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

Yet another embodiment of the present invention is directed to a method of therapeutically treating a mammal having a cancerous tumor comprising cells that express a TAT polypeptide, wherein the method comprises administering to the mammal a therapeutically effective amount of an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby resulting in the effective therapeutic treatment of the tumor. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

Yet another embodiment of the present invention is directed to a method of determining the presence of a TAT polypeptide in a sample suspected of containing the TAT polypeptide, wherein the method comprises exposing the sample to an antibody, oligopeptide or small organic molecule that binds to the TAT polypeptide and determining binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide in the sample, wherein the presence of such binding is indicative of the presence of the TAT polypeptide in the sample. Optionally, the sample may contain cells (which may be cancer cells) suspected of expressing the TAT polypeptide. The antibody, TAT binding oligopeptide or TAT binding organic molecule employed in the method may optionally be detectably labeled, attached to a solid support, or the like.

A further embodiment of the present invention is directed to a method of diagnosing the presence of a tumor in a mammal, wherein the method comprises detecting the level of expression of a gene encoding a TAT polypeptide (a) in a test sample of tissue cells obtained from said mammal, and (b) in a control sample of known normal non-cancerous cells of the same tissue origin or type, wherein a higher level of expression of the TAT polypeptide in the test sample, as compared to the control sample, is indicative of the presence of

tumor in the mammal from which the test sample was obtained.

Another embodiment of the present invention is directed to a method of diagnosing the presence of a tumor in a mammal, wherein the method comprises (a) contacting a test sample comprising tissue cells obtained from the mammal with an antibody, oligopeptide or small organic molecule that binds to a TAT polypeptide and (b) detecting the formation of a complex between the antibody, oligopeptide or small organic molecule and the TAT polypeptide in the test sample, wherein the formation of a complex is indicative of the presence of a tumor in the mammal. Optionally, the antibody, TAT binding oligopeptide or TAT binding organic molecule employed is detectably labeled, attached to a solid support, or the like, and/or the test sample of tissue cells is obtained from an individual suspected of having a cancerous tumor.

Yet another embodiment of the present invention is directed to a method for treating or preventing a cell proliferative disorder associated with altered, preferably increased, expression or activity of a TAT polypeptide, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a TAT polypeptide. Preferably, the cell proliferative disorder is cancer and the antagonist of the TAT polypeptide is an anti-TAT polypeptide antibody, TAT binding oligopeptide, TAT binding organic molecule or antisense oligonucleotide. Effective treatment or prevention of the cell proliferative disorder may be a result of direct killing or growth inhibition of cells that express a TAT polypeptide or by antagonizing the cell growth potentiating activity of a TAT polypeptide.

Yet another embodiment of the present invention is directed to a method of binding an antibody, oligopeptide or small organic molecule to a cell that expresses a TAT polypeptide, wherein the method comprises contacting a cell that expresses a TAT polypeptide with said antibody, oligopeptide or small organic molecule under conditions which are suitable for binding of the antibody, oligopeptide or small organic molecule to said TAT polypeptide and allowing binding therebetween.

Other embodiments of the present invention are directed to the use of (a) a TAT polypeptide, (b) a nucleic acid encoding a TAT polypeptide or a vector or host cell comprising that nucleic acid, (c) an anti-TAT polypeptide antibody, (d) a TAT-binding oligopeptide, or (e) a TAT-binding small organic molecule in the preparation of a medicament useful for (i) the therapeutic treatment or diagnostic detection of a cancer or tumor, or (ii) the therapeutic treatment or prevention of a cell proliferative disorder.

Another embodiment of the present invention is directed to a method for inhibiting the growth of a cancer cell, wherein the growth of said cancer cell is at least in part dependent upon the growth potentiating effect(s) of a TAT polypeptide (wherein the TAT polypeptide may be expressed either by the cancer cell itself or a cell that produces polypeptide(s) that have a growth potentiating effect on cancer cells), wherein the method comprises contacting the TAT polypeptide with an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby antagonizing the growth-potentiating activity of the TAT polypeptide and, in turn, inhibiting the growth of the cancer cell. Preferably the growth of the cancer cell is completely inhibited. Even more preferably, binding of the antibody, oligopeptide or small organic molecule to the TAT polypeptide induces the death of the cancer cell. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present

invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and TAT binding oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

Yet another embodiment of the present invention is directed to a method of therapeutically treating a tumor in a mammal, wherein the growth of said tumor is at least in part dependent upon the growth potentiating effect(s) of a TAT polypeptide, wherein the method comprises administering to the mammal a therapeutically effective amount of an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby antagonizing the growth potentiating activity of said TAT polypeptide and resulting in the effective therapeutic treatment of the tumor. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

C. Further Additional Embodiments

In yet further embodiments, the invention is directed to the following set of potential claims for this application:

1. Isolated nucleic acid having a nucleotide sequence that has at least 80% nucleic acid sequence identity to:

(a) a DNA molecule encoding the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) a DNA molecule encoding the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) a DNA molecule encoding an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) a DNA molecule encoding an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78);

(f) the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(g) the complement of (a), (b), (c), (d), (e) or (f).

2. Isolated nucleic acid having:

(a) a nucleotide sequence that encodes the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) a nucleotide sequence that encodes the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) a nucleotide sequence that encodes an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) a nucleotide sequence that encodes an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78);

(f) the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(g) the complement of (a), (b), (c), (d), (e) or (f).

3. Isolated nucleic acid that hybridizes to:

(a) a nucleic acid that encodes the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) a nucleic acid that encodes the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) a nucleic acid that encodes an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) a nucleic acid that encodes an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78);

(f) the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(g) the complement of (a), (b), (c), (d), (e) or (f).

4. The nucleic acid of Claim 3, wherein the hybridization occurs under stringent conditions.

5. The nucleic acid of Claim 3 which is at least about 5 nucleotides in length.

6. An expression vector comprising the nucleic acid of Claim 1, 2 or 3.

7. The expression vector of Claim 6, wherein said nucleic acid is operably linked to control sequences recognized by a host cell transformed with the vector.

8. A host cell comprising the expression vector of Claim 7.

9. The host cell of Claim 8 which is a CHO cell, an *E. coli* cell or a yeast cell.

10. A process for producing a polypeptide comprising culturing the host cell of Claim 8 under conditions suitable for expression of said polypeptide and recovering said polypeptide from the cell culture.

11. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

12. An isolated polypeptide having:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

13. A chimeric polypeptide comprising the polypeptide of Claim 11 or 12 fused to a heterologous polypeptide.

14. The chimeric polypeptide of Claim 13, wherein said heterologous polypeptide is an epitope tag sequence or an Fc region of an immunoglobulin.

15. An isolated antibody that binds to a polypeptide having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

16. An isolated antibody that binds to a polypeptide having:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

17. The antibody of Claim 15 or 16 which is a monoclonal antibody.

18. The antibody of Claim 15 or 16 which is an antibody fragment.

19. The antibody of Claim 15 or 16 which is a chimeric or a humanized antibody.

20. The antibody of Claim 15 or 16 which is conjugated to a growth inhibitory agent.

21. The antibody of Claim 15 or 16 which is conjugated to a cytotoxic agent.

22. The antibody of Claim 21, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

23. The antibody of Claim 21, wherein the cytotoxic agent is a toxin.

24. The antibody of Claim 23, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

25. The antibody of Claim 23, wherein the toxin is a maytansinoid.

26. The antibody of Claim 15 or 16 which is produced in bacteria.

27. The antibody of Claim 15 or 16 which is produced in CHO cells.

28. The antibody of Claim 15 or 16 which induces death of a cell to which it binds.

29. The antibody of Claim 15 or 16 which is detectably labeled.

30. An isolated nucleic acid having a nucleotide sequence that encodes the antibody of Claim 15 or 16.

31. An expression vector comprising the nucleic acid of Claim 30 operably linked to control sequences recognized by a host cell transformed with the vector.

32. A host cell comprising the expression vector of Claim 31.

33. The host cell of Claim 32 which is a CHO cell, an *E. coli* cell or a yeast cell.

34. A process for producing an antibody comprising culturing the host cell of Claim 32 under conditions suitable for expression of said antibody and recovering said antibody from the cell culture.

35. An isolated oligopeptide that binds to a polypeptide having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

36. An isolated oligopeptide that binds to a polypeptide having:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

37. The oligopeptide of Claim 35 or 36 which is conjugated to a growth inhibitory agent.

38. The oligopeptide of Claim 35 or 36 which is conjugated to a cytotoxic agent.

39. The oligopeptide of Claim 38, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

40. The oligopeptide of Claim 38, wherein the cytotoxic agent is a toxin.

41. The oligopeptide of Claim 40, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

42. The oligopeptide of Claim 40, wherein the toxin is a maytansinoid.

43. The oligopeptide of Claim 35 or 36 which induces death of a cell to which it binds.

44. The oligopeptide of Claim 35 or 36 which is detectably labeled.

45. A TAT binding organic molecule that binds to a polypeptide having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS.1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

46. The organic molecule of Claim 45 that binds to a polypeptide having:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

47. The organic molecule of Claim 45 or 46 which is conjugated to a growth inhibitory agent.

48. The organic molecule of Claim 45 or 46 which is conjugated to a cytotoxic agent.

49. The organic molecule of Claim 48, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

50. The organic molecule of Claim 48, wherein the cytotoxic agent is a toxin.

51. The organic molecule of Claim 50, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

52. The organic molecule of Claim 50, wherein the toxin is a maytansinoid.

53. The organic molecule of Claim 45 or 46 which induces death of a cell to which it binds.

54. The organic molecule of Claim 45 or 46 which is detectably labeled.

55. A composition of matter comprising:

(a) the polypeptide of Claim 11;

(b) the polypeptide of Claim 12;

(c) the chimeric polypeptide of Claim 13;

(d) the antibody of Claim 15;

(e) the antibody of Claim 16;

(f) the oligopeptide of Claim 35;

(g) the oligopeptide of Claim 36;

(h) the TAT binding organic molecule of Claim 45; or

(i) the TAT binding organic molecule of Claim 46; in combination with a carrier.

56. The composition of matter of Claim 55, wherein said carrier is a pharmaceutically acceptable carrier.

57. An article of manufacture comprising:

(a) a container; and

(b) the composition of matter of Claim 55 contained within said container.

58. The article of manufacture of Claim 57 further comprising a label affixed to said container, or a package insert included with said container, referring to the use of said composition of matter for the therapeutic treatment of or the diagnostic detection of a cancer.

59. A method of inhibiting the growth of a cell that expresses a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78), said method comprising contacting said cell with an antibody, oligopeptide or organic molecule that binds to said protein, the binding of said antibody, oligopeptide or organic molecule to said protein thereby causing an inhibition of growth of said cell.

60. The method of Claim 59, wherein said antibody is a monoclonal antibody.

61. The method of Claim 59, wherein said antibody is an antibody fragment.

62. The method of Claim 59, wherein said antibody is a chimeric or a humanized antibody.

63. The method of Claim 59, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

64. The method of Claim 59, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

65. The method of Claim 64, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

66. The method of Claim 64, wherein the cytotoxic agent is a toxin.

67. The method of Claim 66, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

68. The method of Claim 66, wherein the toxin is a maytansinoid.

69. The method of Claim 59, wherein said antibody is produced in bacteria.

70. The method of Claim 59, wherein said antibody is produced in CHO cells.

71. The method of Claim 59, wherein said cell is a cancer cell.

72. The method of Claim 71, wherein said cancer cell is further exposed to radiation treatment or a chemotherapeutic agent.

73. The method of Claim 71, wherein said cancer cell is selected from the group consisting of a breast cancer cell, a colorectal cancer cell, a lung cancer cell, an ovarian cancer cell, a central nervous system cancer cell, a liver cancer cell, a bladder cancer cell, a pancreatic cancer cell, a cervical cancer cell, a melanoma cell and a leukemia cell.

74. The method of Claim 71, wherein said protein is more abundantly expressed by said cancer cell as compared to a normal cell of the same tissue origin.

75. The method of Claim 59 which causes the death of said cell.

76. The method of Claim 59, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

77. A method of therapeutically treating a mammal having a cancerous tumor comprising cells that express a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78), said method comprising administering to said mammal a therapeutically effective amount of an antibody, oligopeptide or organic molecule that binds to said protein, thereby effectively treating said mammal.

78. The method of Claim 77, wherein said antibody is a monoclonal antibody.

79. The method of Claim 77, wherein said antibody is an antibody fragment.

80. The method of Claim 77, wherein said antibody is a chimeric or a humanized antibody.

81. The method of Claim 77, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

82. The method of Claim 77, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

83. The method of Claim 82, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

84. The method of Claim 82, wherein the cytotoxic agent is a toxin.

85. The method of Claim 84, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

86. The method of Claim 84, wherein the toxin is a maytansinoid.

87. The method of Claim 77, wherein said antibody is produced in bacteria.

88. The method of Claim 77, wherein said antibody is produced in CHO cells.

89. The method of Claim 77, wherein said tumor is further exposed to radiation treatment or a chemotherapeutic agent.

90. The method of Claim 77, wherein said tumor is a breast tumor, a colorectal tumor, a lung tumor, an ovarian tumor, a central nervous system tumor, a liver tumor, a bladder tumor, a pancreatic tumor, or a cervical tumor.

91. The method of Claim 77, wherein said protein is more abundantly expressed by the cancerous cells of said tumor as compared to a normal cell of the same tissue origin.

92. The method of Claim 77, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

93. A method of determining the presence of a protein in a sample suspected of containing said protein, wherein said protein has at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78), said method comprising exposing said sample to an antibody, oligopeptide or organic molecule that binds to said protein and determining binding of said antibody, oligopeptide or organic molecule to said protein in said sample, wherein binding of the antibody, oligopeptide or organic molecule to said protein is indicative of the presence of said protein in said sample.

94. The method of Claim 93, wherein said sample comprises a cell suspected of expressing said protein.

95. The method of Claim 94, wherein said cell is a cancer cell.

96. The method of Claim 93, wherein said antibody, oligopeptide or organic molecule is detectably labeled.

97. The method of Claim 93, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

98. A method of diagnosing the presence of a tumor in a mammal, said method comprising determining the level of expression of a gene encoding a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78), in a test sample of tissue cells obtained from said mammal and in a control sample of known normal cells of the same tissue origin, wherein a higher level of expression of said protein in the test sample, as compared to the control sample, is indicative of the presence of tumor in the mammal from which the test sample was obtained.

99. The method of Claim 98, wherein the step of determining the level of expression of a gene encoding said protein comprises employing an oligonucleotide in an *in situ* hybridization or RT-PCR analysis.

100. The method of Claim 98, wherein the step determining the level of expression of a gene encoding said protein comprises employing an antibody in an immunohistochemistry or Western blot analysis.

101. The method of Claim 98, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

102. A method of diagnosing the presence of a tumor in a mammal, said method comprising contacting a test sample of tissue cells obtained from said mammal with an antibody, oligopeptide or organic molecule that binds to a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78), and detecting the formation of a complex between said antibody, oligopeptide or organic molecule and said protein in the test sample, wherein the formation of a

complex is indicative of the presence of a tumor in said mammal.

103. The method of Claim 102, wherein said antibody, oligopeptide or organic molecule is detectably labeled.

104. The method of Claim 102, wherein said test sample of tissue cells is obtained from an individual suspected of having a cancerous tumor.

105. The method of Claim 102, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

106. A method for treating or preventing a cell proliferative disorder associated with increased expression or activity of a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78), said method comprising administering to a subject in need of such treatment an effective amount of an antagonist of said protein, thereby effectively treating or preventing said cell proliferative disorder.

107. The method of Claim 106, wherein said cell proliferative disorder is cancer.

108. The method of Claim 106, wherein said antagonist is an anti-TAT polypeptide antibody, TAT binding oligopeptide, TAT binding organic molecule or antisense oligonucleotide.

109. A method of binding an antibody, oligopeptide or organic molecule to a cell that expresses a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78), said method comprising contacting said cell with an antibody, oligopeptide or organic molecule that binds to said protein and allowing the binding of the antibody, oligopeptide or organic molecule to said protein to occur, thereby binding said antibody, oligopeptide or organic molecule to said cell.

110. The method of Claim 109, wherein said antibody is a monoclonal antibody.

111. The method of Claim 109, wherein said antibody is an antibody fragment.

112. The method of Claim 109, wherein said antibody is a chimeric or a humanized antibody.

113. The method of Claim 109, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

114. The method of Claim 109, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

115. The method of Claim 114, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

116. The method of Claim 114, wherein the cytotoxic agent is a toxin.

117. The method of Claim 116, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

118. The method of Claim 116, wherein the toxin is a maytansinoid.

119. The method of Claim 109, wherein said antibody is produced in bacteria.

120. The method of Claim 109, wherein said antibody is produced in CHO cells.

121. The method of Claim 109, wherein said cell is a cancer cell.

122. The method of Claim 121, wherein said cancer cell is further exposed to radiation treatment or a chemotherapeutic agent.

123. The method of Claim 121, wherein said cancer cell is selected from the group consisting of a breast cancer cell, a colorectal cancer cell, a lung cancer cell, an ovarian cancer cell, a central nervous system cancer cell, a liver cancer cell, a bladder cancer cell, a pancreatic cancer cell, a cervical cancer cell, a melanoma cell and a leukemia cell.

124. The method of Claim 123, wherein said protein is more abundantly expressed by said cancer cell as compared to a normal cell of the same tissue origin.

125. The method of Claim 109 which causes the death of said cell.

126. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

127. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for treating a tumor.

128. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

129. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

130. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of medicament for treating a tumor.

131. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

132. Use of a host cell as claimed in any of Claims 8, 9, 32, or 33 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

133. Use of a host cell as claimed in any of Claims 8, 9, 32 or 33 in the preparation of a medicament for treating a tumor.

134. Use of a host cell as claimed in any of Claims 8, 9, 32 or 33 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

135. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

136. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for treating a tumor.

137. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

138. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

139. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for treating a tumor.

140. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

141. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

142. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for treating a tumor.

143. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

144. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

145. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 58 in the preparation of a medicament for treating a tumor.

146. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

147. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

148. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for treating a tumor.

149. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

150. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

151. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for treating a tumor.

152. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

153. A method for inhibiting the growth of a cell, wherein the growth of said cell is at least in part dependent upon a growth potentiating effect of a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78), said method comprising contacting said protein with an antibody, oligopeptide or organic molecule that binds to said protein, there by inhibiting the growth of said cell.

154. The method of Claim 153, wherein said cell is a cancer cell.

155. The method of Claim 153, wherein said protein is expressed by said cell.

156. The method of Claim 153, wherein the binding of said antibody, oligopeptide or organic molecule to said protein antagonizes a cell growth-potentiating activity of said protein.

157. The method of Claim 153, wherein the binding of said antibody, oligopeptide or organic molecule to said protein induces the death of said cell.

158. The method of Claim 153, wherein said antibody is a monoclonal antibody.

159. The method of Claim 153, wherein said antibody is an antibody fragment.

160. The method of Claim 153, wherein said antibody is a chimeric or a humanized antibody.

161. The method of Claim 153, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

162. The method of Claim 153, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

163. The method of Claim 162, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

164. The method of Claim 162, wherein the cytotoxic agent is a toxin.

165. The method of Claim 164, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

166. The method of Claim 164, wherein the toxin is a maytansinoid.

167. The method of Claim 153, wherein said antibody is produced in bacteria.

168. The method of Claim 153, wherein said antibody is produced in CHO cells.

169. The method of Claim 153, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

170. A method of therapeutically treating a tumor in a mammal, wherein the growth of said tumor is at least in part dependent upon a growth potentiating effect of a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78), said method comprising contacting said protein with an antibody, oligopeptide or organic molecule that binds to said protein, thereby effectively treating said tumor.

171. The method of Claim 170, wherein said protein is expressed by cells of said tumor.

172. The method of Claim 170, wherein the binding of said antibody, oligopeptide or organic molecule to said protein antagonizes a cell growth-potentiating activity of said protein.

173. The method of Claim 170, wherein said antibody is a monoclonal antibody.

174. The method of Claim 170, wherein said antibody is an antibody fragment.

175. The method of Claim 170, wherein said antibody is a chimeric or a humanized antibody.

176. The method of Claim 170, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

177. The method of Claim 170, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

178. The method of Claim 177, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

179. The method of Claim 177, wherein the cytotoxic agent is a toxin.

180. The method of Claim 179, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

181. The method of Claim 179, wherein the toxin is a maytansinoid.

182. The method of Claim 170, wherein said antibody is produced in bacteria.

183. The method of Claim 170, wherein said antibody is produced in CHO cells.

184. The method of Claim 170, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);

(b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).

Yet further embodiments of the present invention will be evident to the skilled artisan upon a reading of the present specification.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a TAT161 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA77507".

Figures 2A-B show a nucleotide sequence (SEQ ID NO:2) of a TAT101 cDNA, wherein SEQ ID NO:2 is a clone designated herein as "DNA80894".

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) of a TAT157 cDNA, wherein SEQ ID NO:3 is a clone designated herein as "DNA82343".

Figure 4 shows a nucleotide sequence (SEQ ID NO:4) of a TAT160 cDNA, wherein SEQ ID NO:4 is a clone designated herein as "DNA87994".

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) of a TAT158 cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA88131".

Figure 6 shows a nucleotide sequence (SEQ ID NO:6) of a TAT110 cDNA, wherein SEQ ID NO:6 is a clone designated herein as "DNA95930".

Figure 7 shows a nucleotide sequence (SEQ ID NO:7) of a TAT210 cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA95930-1".

Figure 8 shows a nucleotide sequence (SEQ ID NO:8) of a TAT159 cDNA, wherein SEQ ID NO:8 is a clone designated herein as "DNA96917".

Figure 9 shows a nucleotide sequence (SEQ ID NO:9) of a TAT112 cDNA, wherein SEQ ID NO:9 is a clone designated herein as "DNA96930".

Figure 10 shows a nucleotide sequence (SEQ ID NO:10) of a TAT147 cDNA, wherein SEQ ID NO:10 is a clone designated herein as "DNA96936".

Figure 11 shows a nucleotide sequence (SEQ ID NO:11) of a TAT145 cDNA, wherein SEQ ID NO:11 is a clone designated herein as "DNA98565".

Figure 12 shows a nucleotide sequence (SEQ ID NO:12) of a TAT152 cDNA, wherein SEQ ID NO:12 is a clone designated herein as "DNA246435".

Figure 13 shows a nucleotide sequence (SEQ ID NO:13) of a TAT162 cDNA, wherein SEQ ID NO:13 is a clone designated herein as "DNA98591".

Figure 14 shows a nucleotide sequence (SEQ ID NO:14) of a TAT114 cDNA, wherein SEQ ID NO:14 is a clone designated herein as "DNA108809".

Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a TAT119 cDNA, wherein SEQ ID NO:15 is a clone designated herein as "DNA119488".

Figure 16 shows a nucleotide sequence (SEQ ID NO:16) of a TAT103 cDNA, wherein SEQ ID NO:16 is a clone designated herein as "DNA143493".

Figures 17A-B show a nucleotide sequence (SEQ ID NO:17) of a TAT130 cDNA, wherein SEQ ID NO:17 is a clone designated herein as "DNA167234".

Figure 18 shows a nucleotide sequence (SEQ ID NO:18) of a TAT166 cDNA, wherein SEQ ID NO:18 is a clone designated herein as "DNA235621".

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a TAT132 cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA176766".

Figure 20 shows a nucleotide sequence (SEQ ID NO:20) of a TAT150 cDNA, wherein SEQ ID NO:20 is a clone designated herein as "DNA236463".

Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a TAT129 cDNA, wherein SEQ ID NO:21 is a clone designated herein as "DNA181162".

Figure 22 shows a nucleotide sequence (SEQ ID NO:22) of a TAT111 cDNA, wherein SEQ ID NO:22 is a clone designated herein as "DNA188221".

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a TAT146 cDNA, wherein SEQ ID NO:23 is a clone designated herein as "DNA233876".

Figure 24 shows a nucleotide sequence (SEQ ID NO:24) of a TAT148 cDNA, wherein SEQ ID NO:24 is a clone designated herein as "DNA193891".

Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a TAT187 cDNA, wherein SEQ ID NO:25 is a clone designated herein as "DNA248170".

Figure 26 shows a nucleotide sequence (SEQ ID NO:26) of a TAT118 cDNA, wherein SEQ ID NO:26 is a clone designated herein as "DNA194628".

Figure 27 shows a nucleotide sequence (SEQ ID NO:27) of a TAT167 cDNA, wherein SEQ ID NO:27 is a clone designated herein as "DNA246415".

Figure 28 shows a nucleotide sequence (SEQ ID NO:28) of a TAT123 cDNA, wherein SEQ ID NO:28 is a clone designated herein as "DNA210499".

Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a TAT211 cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA219894".

Figure 30 shows a nucleotide sequence (SEQ ID NO:30) of a TAT113 cDNA, wherein SEQ ID NO:30 is a clone designated herein as "DNA215609".

Figure 31 shows a nucleotide sequence (SEQ ID NO:31) of a TAT128 cDNA, wherein SEQ ID NO:31 is a clone designated herein as "DNA220432".

Figures 32A-B show a nucleotide sequence (SEQ ID NO:32) of a TAT164 cDNA, wherein SEQ ID NO:32 is a clone designated herein as "DNA226094".

Figure 33 shows a nucleotide sequence (SEQ ID NO:33) of a TAT122 cDNA, wherein SEQ ID NO:33 is a clone designated herein as "DNA226165".

Figure 34 shows a nucleotide sequence (SEQ ID NO:34) of a TAT117 cDNA, wherein SEQ ID NO:34 is a clone designated herein as "DNA226237".

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) of a TAT168 cDNA, wherein SEQ ID NO:35 is a clone designated herein as "DNA246450".

Figure 36 shows a nucleotide sequence (SEQ ID NO:36) of a TAT144 cDNA, wherein SEQ ID NO:36 is a clone designated herein as "DNA226456".

Figure 37 shows a nucleotide sequence (SEQ ID NO:37) of a TAT188 cDNA, wherein SEQ ID NO:37 is a clone designated herein as "DNA237637".

Figure 38 shows a nucleotide sequence (SEQ ID NO:38) of a TAT126 cDNA, wherein SEQ ID NO:38 is a clone designated herein as "DNA226539".

Figure 39 shows a nucleotide sequence (SEQ ID NO:39) of a TAT151 cDNA, wherein SEQ ID NO:39 is a clone designated herein as "DNA236511".

Figure 40 shows a nucleotide sequence (SEQ ID NO:40) of a TAT115 cDNA, wherein SEQ ID NO:40 is a clone designated herein as "DNA226771".

Figure 41 shows a nucleotide sequence (SEQ ID NO:41) of a TAT163 cDNA, wherein SEQ ID NO:41 is a clone designated herein as "DNA227087".

Figure 42 shows a nucleotide sequence (SEQ ID NO:42) of a TAT227 cDNA, wherein SEQ ID NO:42 is a clone designated herein as "DNA266307".

Figure 43 shows a nucleotide sequence (SEQ ID NO:43) of a TAT228 cDNA, wherein SEQ ID NO:43 is a clone designated herein as "DNA266311".

Figure 44 shows a nucleotide sequence (SEQ ID NO:44) of a TAT229 cDNA, wherein SEQ ID NO:44 is a clone designated herein as "DNA266312".

Figure 45 shows a nucleotide sequence (SEQ ID NO:45) of a TAT230 cDNA, wherein SEQ ID NO:45 is a clone designated herein as "DNA266313".

Figure 46 shows a nucleotide sequence (SEQ ID NO:46) of a TAT121 cDNA, wherein SEQ ID NO:46 is a clone designated herein as "DNA227224".

Figure 47 shows a nucleotide sequence (SEQ ID NO:47) of a TAT183 cDNA, wherein SEQ ID NO:47 is a clone designated herein as "DNA247486".

Figure 48 shows a nucleotide sequence (SEQ ID NO:48) of a TAT165 cDNA, wherein SEQ ID NO:48 is a clone designated herein as "DNA227578".

Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a TAT131 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA227800".

Figure 50 shows a nucleotide sequence (SEQ ID NO:50) of a TAT140 cDNA, wherein SEQ ID NO:50 is a clone designated herein as "DNA227904".

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a TAT127 cDNA, wherein SEQ ID NO:51 is a clone designated herein as "DNA228199".

Figure 52 shows a nucleotide sequence (SEQ ID NO:52) of a TAT116 cDNA, wherein SEQ ID NO:52 is a clone designated herein as "DNA228201".

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) of a TAT189 cDNA, wherein SEQ ID NO:53 is a clone designated herein as "DNA247488".

Figure 54 shows a nucleotide sequence (SEQ ID NO:54) of a TAT190 cDNA, wherein SEQ ID NO:54 is a clone designated herein as "DNA236538".

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) of a TAT191 cDNA, wherein SEQ ID NO:55 is a clone designated herein as "DNA247489".

Figure 56 shows a nucleotide sequence (SEQ ID NO:56) of a TAT133 cDNA, wherein SEQ ID NO:56 is a clone designated herein as "DNA228211".

Figure 57 shows a nucleotide sequence (SEQ ID NO:57) of a TAT186 cDNA, wherein SEQ ID NO:57 is a clone designated herein as "DNA233937".

Figure 58 shows a nucleotide sequence (SEQ ID NO:58) of a TAT120 cDNA, wherein SEQ ID NO:58 is a clone designated herein as "DNA228993".

Figure 59 shows a nucleotide sequence (SEQ ID NO:59) of a TAT124 cDNA, wherein SEQ ID NO:59 is a clone designated herein as "DNA228994".

Figure 60 shows a nucleotide sequence (SEQ ID NO:60) of a TAT105 cDNA, wherein SEQ ID NO:60 is a clone designated herein as "DNA229410".

Figures 61A-B show a nucleotide sequence (SEQ ID NO:61) of a TAT107 cDNA, wherein SEQ ID NO:61 is a clone designated herein as "DNA229411".

Figures 62A-B show a nucleotide sequence (SEQ ID NO:62) of a TAT108 cDNA, wherein SEQ ID NO:62 is a clone designated herein as "DNA229413".

Figures 63A-B show a nucleotide sequence (SEQ ID NO:63) of a TAT139 cDNA, wherein SEQ ID NO:63 is a clone designated herein as "DNA229700".

Figure 64 shows a nucleotide sequence (SEQ ID NO:64) of a TAT143 cDNA, wherein SEQ ID NO:64 is a clone designated herein as "DNA231512".

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) of a TAT100 cDNA, wherein SEQ ID NO:65 is a clone designated herein as "DNA231542".

Figure 66 shows a nucleotide sequence (SEQ ID NO:66) of a TAT284 cDNA, wherein SEQ ID NO:66 is a clone designated herein as "DNA231542-1".

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) of a TAT285 cDNA, wherein SEQ ID NO:67 is a clone designated herein as "DNA231542-2".

Figure 68 shows a nucleotide sequence (SEQ ID NO:68) of a TAT285-1 cDNA, wherein SEQ ID NO:68 is a clone designated herein as "DNA297393".

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) of a TAT125 cDNA, wherein SEQ ID NO:69 is a clone designated herein as "DNA232754".

Figure 70 shows a nucleotide sequence (SEQ ID NO:70) of a TAT149 cDNA, wherein SEQ ID NO:70 is a clone designated herein as "DNA234833".

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) of a TAT251 cDNA, wherein SEQ ID NO:71 is a clone designated herein as "DNA268022".

Figure 72 shows a nucleotide sequence (SEQ ID NO:72) of a TAT153 cDNA, wherein SEQ ID NO:72 is a clone designated herein as "DNA236246".

Figure 73 shows a nucleotide sequence (SEQ ID NO:73) of a TAT104 cDNA, wherein SEQ ID NO:73 is a clone designated herein as "DNA236343".

Figure 74 shows a nucleotide sequence (SEQ ID NO:74) of a TAT141 cDNA, wherein SEQ ID NO:74 is a clone designated herein as "DNA236493".

Figure 75 shows a nucleotide sequence (SEQ ID NO:75) of a TAT162 cDNA, wherein SEQ ID NO:75 is a clone designated herein as "DNA236534".

Figure 76 shows a nucleotide sequence (SEQ ID NO:76) of a TAT109 cDNA, wherein SEQ ID NO:76 is a clone designated herein as "DNA246430".

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) of a TAT142 cDNA, wherein SEQ ID NO:77 is a clone designated herein as "DNA247480".

Figures 78A-B show a nucleotide sequence (SEQ ID NO:78) of a TAT106 cDNA, wherein SEQ ID NO:78 is a clone designated herein as "DNA264454".

Figure 79 shows the amino acid sequence (SEQ ID NO:79) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 80 shows the amino acid sequence (SEQ ID NO:80) derived from the coding sequence of SEQ ID NO:2 shown in Figure 2.

Figure 81 shows the amino acid sequence (SEQ ID NO:81) derived from the coding sequence of SEQ ID NO:3 shown in Figure 3.

Figure 82 shows the amino acid sequence (SEQ ID NO:82) derived from the coding sequence of SEQ ID NO:4 shown in Figure 4.

Figure 83 shows the amino acid sequence (SEQ ID NO:83) derived from the coding sequence of SEQ ID NO:5 shown in Figure 5.

Figure 84 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID NO:6 shown in Figure 6.

Figure 85 shows the amino acid sequence (SEQ ID NO:85) derived from the coding sequence of SEQ ID NO:7 shown in Figure 7.

Figure 86 shows the amino acid sequence (SEQ ID NO:86) derived from the coding sequence of SEQ ID NO:8 shown in Figure 8.

Figure 87 shows the amino acid sequence (SEQ ID NO:87) derived from the coding sequence of SEQ ID NO:9 shown in Figure 9.

Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:10 shown in Figure 10.

Figure 89 shows the amino acid sequence (SEQ ID NO:89) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:12 shown in Figure 12.

Figure 91 shows the amino acid sequence (SEQ ID NO:91) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:14 shown in Figure 14.

Figure 93 shows the amino acid sequence (SEQ ID NO:93) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:16 shown in Figure 16.

Figure 95 shows the amino acid sequence (SEQ ID NO:95) derived from the coding sequence of SEQ ID NO:17 shown in Figures 17A-B.

Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:18 shown in Figure 18.

Figure 97 shows the amino acid sequence (SEQ ID NO:97) derived from the coding sequence of SEQ ID NO:19 shown in Figure 19.

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:20 shown in Figure 20.

Figure 99 shows the amino acid sequence (SEQ ID NO:99) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:22 shown in Figure 22.

Figure 101 shows the amino acid sequence (SEQ ID NO:101) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:24 shown in Figure 24.

Figure 103 shows the amino acid sequence (SEQ ID NO:103) derived from the coding sequence of SEQ ID NO:25 shown in Figure 25.

Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ ID NO:26 shown in Figure 26.

Figure 105 shows the amino acid sequence (SEQ ID NO:105) derived from the coding sequence of SEQ ID NO:27 shown in Figure 27.

Figure 106 shows the amino acid sequence (SEQ ID NO:106) derived from the coding sequence of SEQ ID NO:28 shown in Figure 28.

Figure 107 shows the amino acid sequence (SEQ ID NO:107) derived from the coding sequence of SEQ ID NO:29 shown in Figure 29.

Figure 108 shows the amino acid sequence (SEQ ID NO:108) derived from the coding sequence of SEQ ID NO:30 shown in Figure 30.

Figure 109 shows the amino acid sequence (SEQ ID NO:109) derived from the coding sequence of SEQ ID NO:31 shown in Figure 31.

Figures 110A-B shows the amino acid sequence (SEQ ID NO:110) derived from the coding sequence of SEQ ID NO:32 shown in Figures 32A-B.

Figure 111 shows the amino acid sequence (SEQ ID NO:111) derived from the coding sequence of SEQ ID NO:33 shown in Figure 33.

Figure 112 shows the amino acid sequence (SEQ ID NO:112) derived from the coding sequence of SEQ ID NO:34 shown in Figure 34.

Figure 113 shows the amino acid sequence (SEQ ID NO:113) derived from the coding sequence of SEQ ID NO:35 shown in Figure 35.

Figure 114 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:36 shown in Figure 36.

Figure 115 shows the amino acid sequence (SEQ ID NO:115) derived from the coding sequence of SEQ ID NO:37 shown in Figure 37.

Figure 116 shows the amino acid sequence (SEQ ID NO:116) derived from the coding sequence of SEQ ID NO:38 shown in Figure 38.

Figure 117 shows the amino acid sequence (SEQ ID NO:117) derived from the coding sequence of SEQ ID NO:39 shown in Figure 39.

Figure 118 shows the amino acid sequence (SEQ ID NO:118) derived from the coding sequence of SEQ ID NO:40 shown in Figure 40.

Figure 119 shows the amino acid sequence (SEQ ID NO:119) derived from the coding sequence of SEQ ID NO:41 shown in Figure 41.

Figure 120 shows the amino acid sequence (SEQ ID NO:120) derived from the coding sequence of SEQ ID NO:42 shown in Figure 42.

Figure 121 shows the amino acid sequence (SEQ ID NO:121) derived from the coding sequence of SEQ ID NO:43 shown in Figure 43.

Figure 122 shows the amino acid sequence (SEQ ID NO:122) derived from the coding sequence of SEQ ID NO:44 shown in Figure 44.

Figure 123 shows the amino acid sequence (SEQ ID NO:123) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45.

Figure 124 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:46 shown in Figure 46.

Figure 125 shows the amino acid sequence (SEQ ID NO:125) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:48 shown in Figure 48.

Figure 127 shows the amino acid sequence (SEQ ID NO:127) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:50 shown in Figure 50.

Figure 129 shows the amino acid sequence (SEQ ID NO:129) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:52 shown in Figure 52.

Figure 131 shows the amino acid sequence (SEQ ID NO:131) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 132 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:54 shown in Figure 54.

Figure 133 shows the amino acid sequence (SEQ ID NO:133) derived from the coding sequence of SEQ ID NO:55 shown in Figure 55.

Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ ID NO:56 shown in Figure 56.

Figure 135 shows the amino acid sequence (SEQ ID NO:135) derived from the coding sequence of SEQ ID NO:57 shown in Figure 57.

Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:58 shown in Figure 58.

Figure 137 shows the amino acid sequence (SEQ ID NO:137) derived from the coding sequence of SEQ ID NO:59 shown in Figure 59.

Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:60 shown in Figure 60.

Figure 139 shows the amino acid sequence (SEQ ID NO:139) derived from the coding sequence of SEQ ID NO:61 shown in Figures 61A-B.

Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:62 shown in Figures 62A-B.

Figure 141 shows the amino acid sequence (SEQ ID NO:141) derived from the coding sequence of SEQ ID NO:63 shown in Figures 63A-B.

Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ ID NO:64 shown in Figure 64.

Figure 143 shows the amino acid sequence (SEQ ID NO:143) derived from the coding sequence of SEQ ID NO:66 shown in Figure 66.

Figure 144 shows the amino acid sequence (SEQ ID NO:144) derived from the coding sequence of SEQ ID NO:67 shown in Figure 67.

Figure 145 shows the amino acid sequence (SEQ ID NO:145) derived from the coding sequence of SEQ ID NO:68 shown in Figure 68.

Figure 146 shows the amino acid sequence (SEQ ID NO:146) derived from the coding sequence of SEQ ID NO:69 shown in Figure 69.

Figure 147 shows the amino acid sequence (SEQ ID NO:147) derived from the coding sequence of SEQ ID NO:70 shown in Figure 70.

Figure 148 shows the amino acid sequence (SEQ ID NO:148) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

Figure 149 shows the amino acid sequence (SEQ ID NO:149) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

Figure 150 shows the amino acid sequence (SEQ ID NO:150) derived from the coding sequence of SEQ ID NO:74 shown in Figure 74.

Figure 151 shows the amino acid sequence (SEQ ID NO:151) derived from the coding sequence of SEQ ID NO:75 shown in Figure 75.

Figure 152 shows the amino acid sequence (SEQ ID NO:152) derived from the coding sequence of SEQ ID NO:76 shown in Figure 76.

Figure 153 shows the amino acid sequence (SEQ ID NO:153) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 154 shows the amino acid sequence (SEQ ID NO:154) derived from the coding sequence of SEQ ID NO:78 shown in Figures 78A-B.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

The terms "TAT polypeptide" and "TAT" as used herein and when immediately followed by a numerical designation, refer to various polypeptides, wherein the complete designation (i.e., TAT/number) refers to specific polypeptide sequences as described herein. The terms "TAT/number polypeptide" and "TAT/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides, polypeptide variants and fragments of native sequence polypeptides and polypeptide variants (which are further defined herein). The TAT polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "TAT polypeptide" refers to each individual TAT/number polypeptide disclosed herein. All disclosures in this specification which refer to the "TAT polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, formation of TAT binding oligopeptides to or against, formation of TAT binding organic molecules to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "TAT polypeptide" also includes variants of the TAT/number polypeptides disclosed herein.

A "native sequence TAT polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding TAT polypeptide derived from nature. Such native sequence TAT polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence TAT polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific TAT polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In certain embodiments of the invention, the native sequence TAT polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons (if indicated) are shown in bold font and underlined in the figures. Nucleic acid residues indicated as "N" in the accompanying figures are any nucleic acid residue. However, while the TAT polypeptides disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the TAT polypeptides.

The TAT polypeptide "extracellular domain" or "ECD" refers to a form of the TAT polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a TAT polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the TAT polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a TAT polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various TAT polypeptides disclosed herein may be shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"TAT polypeptide variant" means a TAT polypeptide, preferably an active TAT polypeptide, as defined herein having at least about 80% amino acid sequence identity with a full-length native sequence TAT polypeptide sequence as disclosed herein, a TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length TAT polypeptide). Such TAT polypeptide variants include, for instance, TAT polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a TAT polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, to a full-length native sequence TAT polypeptide sequence as disclosed herein, a TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide sequence as disclosed herein. Ordinarily, TAT variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240,

250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 amino acids in length, or more. Optionally, TAT variant polypeptides will have no more than one conservative amino acid substitution as compared to the native TAT polypeptide sequence, alternatively no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitution as compared to the native TAT polypeptide sequence.

"Percent (%) amino acid sequence identity" with respect to the TAT polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific TAT polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "TAT", wherein "TAT" represents the amino acid sequence of a hypothetical TAT polypeptide of interest, "Comparison Protein" represents the amino acid

sequence of a polypeptide against which the "TAT" polypeptide of interest is being compared, and "X," "Y" and "Z" each represent different hypothetical amino acid residues. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

"TAT variant polynucleotide" or "TAT variant nucleic acid sequence" means a nucleic acid molecule which encodes a TAT polypeptide, preferably an active TAT polypeptide, as defined herein and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence TAT polypeptide sequence as disclosed herein, a full-length native sequence TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length TAT polypeptide). Ordinarily, a TAT variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence TAT polypeptide sequence as disclosed herein, a full-length native sequence TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, TAT variant polynucleotides are at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

"Percent (%) nucleic acid sequence identity" with respect to TAT-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the TAT nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user

documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

100 times the fraction W/Z

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "TAT-DNA", wherein "TAT-DNA" represents a hypothetical TAT-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "TAT-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides. Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

In other embodiments, TAT variant polynucleotides are nucleic acid molecules that encode a TAT polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length TAT polypeptide as disclosed herein. TAT variant polypeptides may be those that are encoded by a TAT variant polynucleotide.

The term "full-length coding region" when used in reference to a nucleic acid encoding a TAT polypeptide refers to the sequence of nucleotides which encode the full-length TAT polypeptide of the invention (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures). The term "full-length coding region" when used in reference to an ATCC deposited nucleic acid refers to the TAT polypeptide-encoding portion of the cDNA that is inserted into the vector deposited with the ATCC (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures).

"Isolated," when used to describe the various TAT polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-